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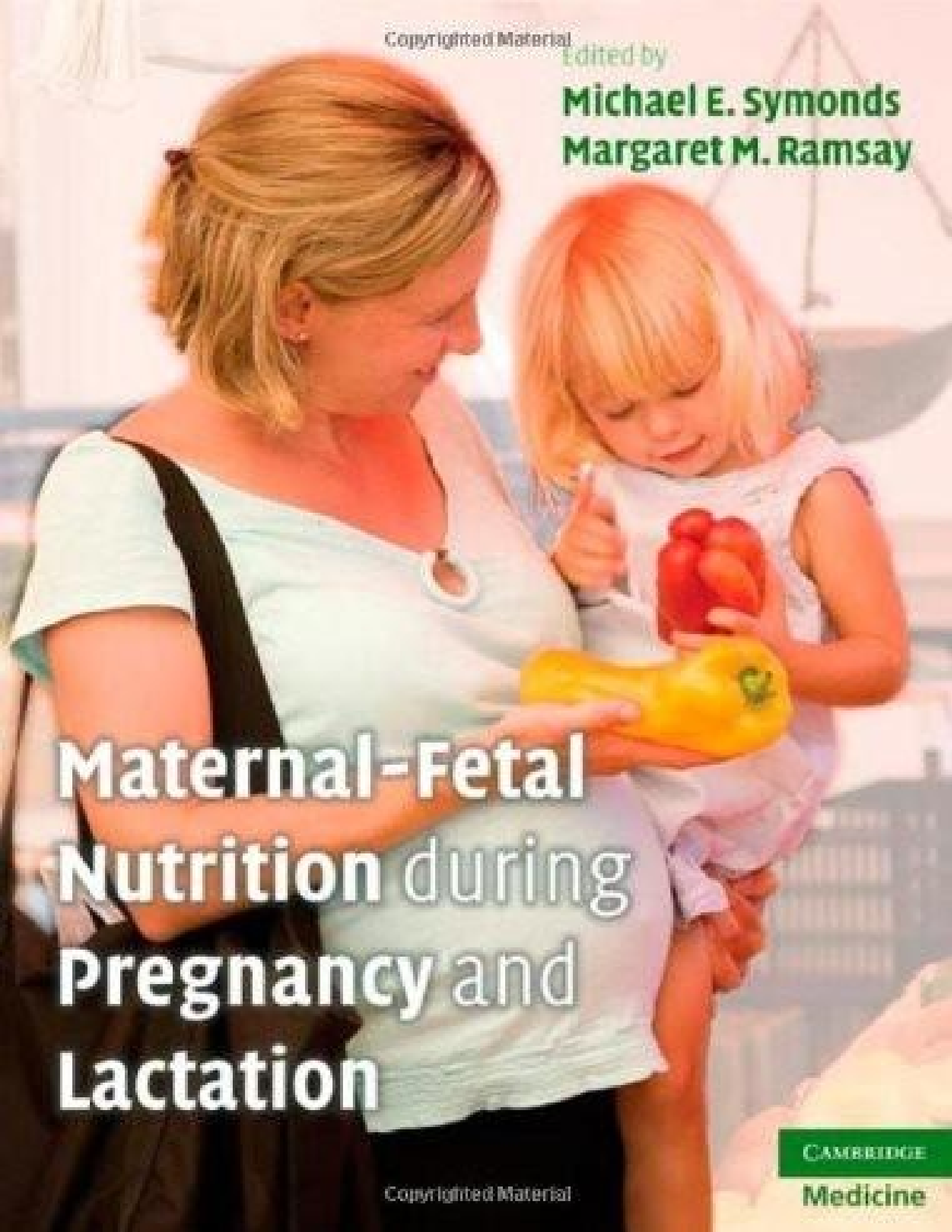

Maternal-Fetal Nutrition during Pregnancy and Lactation

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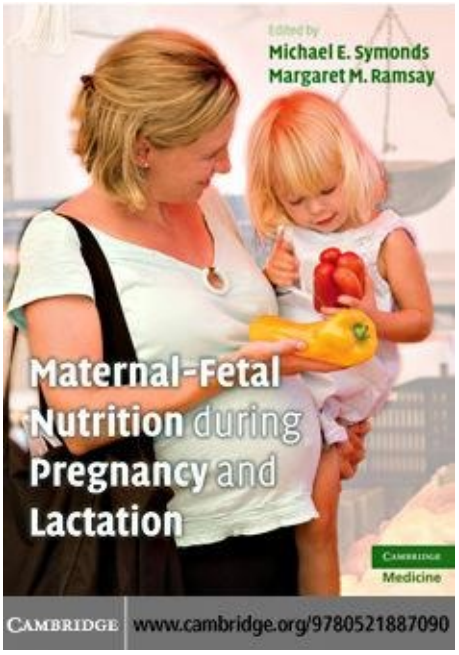

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during Pregnancy and

Lactation

CAMBRIDGE UNIVERSITY PRESS

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Lactation

Editors

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Section 1

Nutritional regulation and requirements for pregnancy and

Chapter

fetal growth

1Maternaladaptationstopregnancyandthe

role of the placenta

Leslie Myatt and Theresa Powell

Delivery of an optimally grown, viable infant defines

within 5 weeks of conception [2]. Blood volume a successful pregnancy. Optimal growth is achieved increases from 6 to 8 weeks gestation onward by

45% to

by the interaction of maternal, placental, and fetal

reach approximately 5 l at 32 weeks gestation [3]. This systems to deliver maternal nutrients to the placenta, increase is greater with multifetal gestation and cor—

transfer them to the fetus, and maximize their utiliza—

relates with fetal weight. The mechanism is unknown

tion for fetal growth. Pregnancy is characterized by

but occurs in the absence of a fetus and may be related

profound changes in the maternal immune, metabolic,

to the renin-angiotensin system or relaxin. Red blood

cardiovascular, and renal systems to ensure a success—

cell mass also increases by 20% to 30% in pregnancy,

ful pregnancy and adequate fetal growth. The fetal—

reflecting increased production of red blood cells, but

placental unit secretes many hormonal signals, the

the net result is physiological hemodilution, poten—

roles of which include redirecting maternal physiol—

tially a protective effect because it reduces blood vis—

ogy and metabolism to direct substrate toward the

cosity to counter the predisposition for thromboem—

fetus and support normal fetal growth. The physio—

bolic events in pregnancy [4] and may also be benefi-logical adaptations of pregnancy begin shortly after cial for placental perfusion.

conception, indeed before the establishment of a fetal—

Cardiac output (heart rate × stroke volume)

placental unit, and thus in their early phases must

increases by 30% to 50% in pregnancy [5] because be directed by maternal signals, including those from of increases in both stroke volume and heart rate.

the corpus luteum. Subsequently feto-placental sig—

The early increase is due to the rise in stroke volume

nals play a major role in regulation of maternal

[5], reflecting the increase in ventricular mass and metabolism. This chapter describes the maternal adap-end-diastolic volume. Stroke volume declines toward tation to pregnancy and the role of the placenta in

term, but heart rate increases from 5 to 32 weeks

nutrient transfer to the fetus.

gestation by 15 to 20 beats per min and is maintained

thereafter to maintain cardiac output. Blood flow

Adaptive changes in maternal

to the uterus increases 10-fold (from 2% to 17% of

cardiac output) in gestation, reaching 500 to 800

physiology

ml/min at term. Arterial blood pressure and systemic

vascular resistance decrease from as early as 5 weeks

Cardiovascular system

gestation and reach a nadir in the second trimester,

The changes in the cardiovascular system seen in preg—

after which blood pressure increases again. This is

nancy are by far the largest physiological challenge

thought to be hormonally regulated, perhaps by

this system will face throughout the life cycle and

progesterone, the endothelial-derived vasodilator

include anatomical changes, increased blood volume

nitric oxide, or prostaglandins, but also potentially by

and cardiac output, and a decrease in systemic vascu—

the introduction of the low-resistance uteroplacental

lar resistance. Ventricular wall muscle mass increases

circulation [6]. The decrease in systemic vascular in the first trimester [1], followed by an increase in resistance may be the stimulus to increase heart rate, end-diastolic volume in the second and early third

stroke volume, and cardiac output in early gestation.

trimesters to increase cardiac compliance. Collagen

Maternal tidal volume increases by 40% in pregnancy,

softening is seen, resulting in increased compliance of

resulting in hyperventilation and a decrease in partial

capacitive and conductive vessels; this change occurs

pressure of carbon dioxide in blood.

1

Section 1: Nutritional regulation and requirements for pregnancy and fetal growth Renal system may have major nongenomic relaxatory effects on the

vasculature [14].

Renal size, weight, and volume increase in gestation

The placenta is also the major site for estrogen

because of increases in renal vascular and interstitial

synthesis. The predominant estrogen in pregnancy is

volume [7] together with a marked increase in dilation estriol, formed as a result of interaction of fetal and of the collecting system. Renal blood flow increases

placental tissues through which fetal adrenal dehy—

60% to 80% by mid-gestation and is 50% greater at

droepiandrosterone sulfate (DHEAS) is converted to

term [8]. Glomerular filtration rate increases up to estrogens by placental sulfatase and aromatase. Pla-50% at the end of the first trimester, with a modest cental estrogen production increases throughout ges—

increase in creatinine clearance. These changes are initation. Estrogen has been shown to have a powerful

tiated in the luteal phase of the menstrual cycle [9]. In effect in increasing uterine blood flow and may there-the rat, there is strong evidence that the ovarian hor- fore facilitate fetal nutrition by increasing placental mone relaxin is responsible for renal hemodynamic

oxygenation and nutrient delivery. It also prepares the

and osmoregulatory changes in pregnancy [10]. Simi-breast for lactation, affects

the renin-angiotensin sys-larly, in humans, relaxin appears to play a role in estab—

tem, and stimulates production of hormone-binding

lishing the renal response [11]. However in the absence globulins in the liver.

of relaxin, as in patients with ovum donation and no

corpus luteum, a renal response, although subdued, is

still seen, suggesting that some other mechanism may

Maternal metabolic changes

also operate. In the luteal phase of the cycle, luteiniz-

in gestation

ing hormone stimulates relaxin secretion from the cor—

During pregnancy, an adaptation of maternal

pus luteum, and this response is augmented and main—

metabolism functions to ensure normal fetal growth

tained by human chorionic gonadotropin (hCG) after

throughout gestation and neonatal growth during

conception.

lactation. Thus, there is a period of adipose tissue

accretion in early gestation followed by insulin resis-

tance to increase glucose availability for the fetus

The concept of the feto-placental unit originated in
and lipolysis to increase fatty acid availability. The
the 1950s but it is now recognized that the placenta
maternal metabolic reprogramming is believed to
and in particular the syncytiotrophoblast is a power—
be directed by placental hormones. Insulin secretion
ful endocrine organ that synthesizes many steroid and
increases during early pregnancy and more than
peptide hormones whose role is to ensure fetal sur—
doubles, resulting in a 30% higher mean insulin level
vival and growth by directing maternal metabolism
by the third trimester. Skeletal muscle, which is the
and fetal growth and development. Human chori—
major site of glucose disposal, and adipose tissue both
onic gonadotropin (hCG) is the earliest biochemical
become highly insulin resistant during the second
marker of pregnancy produced by the embryo (7–
half of pregnancy. There is a 50% reduction in insulin—
8 days after fertilization) and with a doubling time
mediated glucose disposal, requiring an increase
of 31 hours after implantation [12]. The major bio-in insulin secretion to

maintain euglycemia [16].

logical role of hCG in early pregnancy is to rescue

Failure of the mother to increase insulin will lead to

the corpus luteum from demise and maintain pro—

maternal hyperglycemia and thus fetal hyperglycemia

gesterone (and presumably relaxin) production until

with consequent fetal hyperinsulinemia, macrosomia,

the luteal-placental shift in progesterone production

and fetal hypoxia. Insulin also loses its ability to

at 9 weeks gestation. Following this time, the placenta

suppress whole-body lipolysis, leading to increased

is the major source of progesterone synthesis from

postprandial free fatty acid levels and a decline in

maternal cholesterol, reaching 250 mg/day at term

maternal adipose tissue [17]. Total plasma lipids, from 25 mg/day in the luteal phase. The major roles triglycerides, free fatty acids, and cholesterol increase

of progesterone in pregnancy may be in dampening

after 24 weeks gestation [18] with increases in pre-B

immune responses and maintaining smooth muscle

lipoprotein, high-density lipoprotein (HDL) choles—

quiescence. Indeed, in animal species, high circulating

terol in early pregnancy, and low-density lipoprotein

progesterone is associated with myometrial quiescence

(LDL) cholesterol in late pregnancy. The action of

2

and delayed onset of labor [13]. Similarly progesterone insulin is mediated through insulin receptors that are **Chapter 1: Maternal adaptations to pregnancy and the role of the placenta** regulated by phosphorylation. The degree of glucose **The effect of maternal nutrient**

uptake and insulin resistance is also regulated by the

level of insulin receptor substrate-1 (IRS-1) protein

availability

and levels of the p85␣ subunit of phosphoinositide

In light of the low total nutrient requirements in early

3-kinase, which docks to IRS-1 (reviewed by Barbour

pregnancy, data are rapidly accumulating implicating

et al. [19]).

early gestation as a pivotal period for determining placental and fetal growth trajectories. Maternal nutri-

Early pregnancy as a determinant of

ent availability and metabolic status may not be fully

equivalent as determinants of fetal growth, as is appar-

placental and fetal growth

ent in the analysis of exposure to food shortage dur—

Maternal nutrition around the time of conception

ing different periods of gestation for individuals born

may have important effects on gestational length, fetal

around the time of the Dutch famine. In pregnan—

growth trajectory, and postnatal growth and health

cies affected by famine primarily during early gesta-

(for review, see Cross and Mickelson [20]. Specific tion, offspring were of normal size at birth and showed nutrients and general nutritional status of the mother

increased risk for cardiovascular disease later in life

may play key roles in altering the development of

[27]. The early pregnancy effect may be related to the placenta, effects that have direct consequences insufficient fat deposition in the mother during this

on the fetus [21]. Blastocyst development and sub-critical period of pregnancy [28]. Likewise, hypereme-sequent implantation potential are reduced in dia-sis in the first half of pregnancy, which could be consid—

betic mothers and when culturing embryos in high Dered a form of maternal undernutrition in early preg—

glucose [22]. Both essential and nonessential amino nancy, generally results in only small reductions in acids affect mouse blastocyst development during in

birth weight [29]. In pregnancies in which the Dutch vitro culture by enhancing postimplantation develop-famine was experienced later in pregnancy, growth ment and increasing implantation potential [23]. The restriction as well as increased risk for metabolic dis-mammalian target of rapamycin (mTOR) signaling eases in adulthood resulted [30].

pathway mediates the effects of amino acids in stim—

In animal models in which nutrient restriction can
ulating blastocyst growth and invasion. Adequacy of
be manipulated to distinct periods of gestation, dif—
amino acids is detected by the mTOR system, and
ferential long-term effects on the offspring have been
invasive capacity is upregulated if nutrients are avail—
documented. In pregnant sheep, early maternal nutri—
able. Insufficient nutrients result in a lack of invasive—
ent restriction appears to have effects primarily on the
ness, and the implantation window may be lost [24].
brain (smaller brain and impaired cognitive function),
Ghrelin, a hormone known to stimulate appetite, may
whereas maternal nutrient restriction later in preg—
also affect early development. Treatment with ghrelin
nancy results in small fetuses that have an increased
reduces the number of inner cell mass and trophecto—
risk of developing glucose intolerance, insulin resis—
derm cells in blastocysts, similar to the effect of a low
tance, and increased fat mass (for review, see Symonds
protein diet [25].
et al. [31]). These data suggest that nutrient availabil-Once implantation is

successful and the pregnancy ity alone is not the primary factor regulating fetal and

is established, there is little variation in the size of the

placental growth rates or birth weight. In fact, several

human fetus up to 16 weeks gestation, and the early

observational studies suggest that only in quite severe

conceptus has low absolute energetic and anabolic

maternal malnutrition is birth size affected. The bal—

needs. Excluding chromosomal and genetic disorders,

ance of macronutrients in the diet of pregnant women

the dominant determinant of variation in fetal size is

has been suggested to play a role in determining birth

supply of nutrients and oxygen. Early fetal nutrition

weight, with dietary protein in early pregnancy likely

may be provided by endometrial glands that remain

to be an important factor [32]. The metabolic status of functional until at least 10 weeks gestation. These the mother – that is, insulin sensitivity, glycemic con—

glands have intact pathways to the intervillous space

trol, and inflammatory status during the early preg—

and secrete carbohydrates and lipids as well as growth

nancy window – may have profound effects on the

factors, which provide a source of histotrophic nutri—

fetus in utero and later in life. The relationship between

ents and direct the differentiation of the developing vil—

maternal nutritional availability and the mother’s abil-

lous tissue (for review, see Burton *et al.* [26]).

ity to maintain a healthy metabolic environment for

Section 1: Nutritional regulation and requirements for pregnancy and fetal growth her fetus may depend on her nutritional status before link between maternal nutritional status and nutrient

pregnancy [33] or her ability to mobilize stores during delivery to the fetus.

pregnancy. The interaction between maternal nutri—

Nutritionally mediated alterations in epigenetic

tion and metabolic status in pregnancy requires addi—

regulation during gestation may lead to alterations in

tional study.

placental function. Changes in maternal nutrition can

affect the degree of DNA methylation – for example,

Mechanisms linking maternal

through altered availability of methyl donors (folate) in

the diet. This provides an inheritable alteration in gene

nutrition and fetal growth

expression without a change in the DNA sequence and

The genetic contribution to fetal size at birth is pri—
may be important in modifying fetal and placental
marily of maternal origin and may relate to maternal
growth in utero and in developmental origins of adult
size – in particular, maternal height. Although overall
disease [40].
genetic contributions to birth weight are low, the non—
Maternal nutrition also affects both placental and
genetic maternal environmental and phenotypic influ—
fetal vascular development. In pregnant rats, global
ences are more important. Generally speaking, mater—
undernutrition of the dam leads to intrauterine growth
nal nutrition may contribute to fetal growth regulation
restriction (IUGR) and whereas the placental vil—
through several mechanisms.
lous surface area increases to compensate for insuffi—
Insulin-like growth factor 1 (IGF-1) is the primary
cient nutrient delivery from the mother, the extent of
fetal growth–stimulating factor in response to altered
fetal vasculature does not [41]. In experimental iron nutrient supply during late gestation and is under the restriction in rodents, the villous surface area is also

control of fetal insulin [34]. Maternal undernutrition is increased, but fetal vasculature is not [42]. In sheep associated with reduced fetal IGF-1 levels and reduced models of nutrition in pregnancy, both increased and

fetal growth [35].

decreased overall caloric intake leads to IUGR and

Repeat exposure to maternal glucocorticoid leads

fewer, smaller, less vascularized cotyledons [43]. The to growth restriction. The fetus is normally protected developmental signaling systems that lead to changes

by the action of the placental enzyme 11-HSD.

in placental vascular and fetal growth are not yet

This enzyme is downregulated in periods of maternal

clearly defined and are likely to be different for early

undernutrition, which exposes the fetus to maternal

and late gestation. The interaction between develop—

glucocorticoids [36].

mental signaling systems and nutrient availability is

Maternal glycemic control in early pregnancy has

an area that requires investigative attention to define

been shown in both animal models and humans to be

more accurately the exact nature of maternal nutrient

a major factor in predicting fetal growth. In humans,

requirements in early pregnancy.

first-trimester maternal glycosylated hemoglobin

(Hb1AC) is the best predictor of macrosomia in

The role of the placenta in

pregnancies complicated by Type I diabetes [37], suggesting that growth trajectories are established early in **regulation of maternal metabolism**

pregnancy and are responsive to maternal metabolic

and fetal growth

signaling. Similarly, in pregnant rats, episodic hyperglycemia in early but not late pregnancy resulted in

Secretion of human chorionic

placental and fetal overgrowth [38].

Insulin and leptin are maternal metabolic indica—

somatomammotropin and growth hormone

tors that may be involved in fetal intrauterine growth

Human chorionic somatomammotropin (hCS; also

adaptation and long-term health. Decreases in lep—

called human placental lactogen, hPL) has structural

tin and insulin during periods of maternal nutrient

and biological similarities to human growth hormone

restriction or high levels of these hormones in preg-

(hGH) and prolactin. hCS is produced only by syn—

nant obese women may provide a signaling path—

cytiotrophoblast, but production increases 30-fold in

way for altering fetal growth in utero [39]. Both of gestation, reaching 1 to 4 g/day at term. However the these hormones have been shown to regulate placen —

role of hCS is still not fully elucidated. It is suggested to

tal nutrient transport functions, providing a direct

control maternal metabolism, resulting in reductions

Chapter 1: Maternal adaptations to pregnancy and the role of the placenta
Figure 1.1 Schematic representation of maternal adaptation to pregnancy.

Insulin

Resistance

hCG

Glucose

hPL

Lipolysis

Amino Acids

Fatty Acids

in fasting maternal glucose, increased maternal plasma free fatty acids, increased insulin secretion from the pancreas, but insulin resistance and reduced mater—nal glucose uptake to facilitate transfer to the fetus.

Role of adipokines

The term adipokines includes leptin, adiponectin, tumor necrosis factor–alpha (TNF␣), interleukin-6 (IL-6), resistin, and other mediators. These are pro—duced by many cell types including the placenta, mak—ing difficult the dissection of the roles of maternal ver—sus placental synthesis and paracrine versus endocrine action.

Despite its structural similarity, hCS has little growth-promoting and lactogenic activity in humans, and nor—mal pregnancies occur in the near absence of hCS, suggesting that hCS is not essential for pregnancy but serves a redundant function for hGH and prolactin.

Placental GH occurs in nonglycosylated and glyco—

TNF␣, in addition to monocytes, macrophages,

sylated forms and increases six-to eightfold in mater—

and adipocytes, is produced by the placenta. In obese

nal plasma in the second trimester, replacing normal

individuals, there is a positive correlation between

pituitary GH in the maternal circulation. In transgenic

TNF␣ levels, hyperinsulinemia, and body mass index

mice, overexpression of hPGH causes severe periph-

(BMI) [45]. TNF␣ increases insulin resistance when eral insulin resistance [44]. Placental GH may also added to human skeletal muscle cells in culture [46].

stimulate IGF-1 production in maternal liver. Insulin

This may be due to increased phosphorylation of

resistance in pregnancy is associated with maternal

IRS-1 [45] and reduced insulin receptor tyrosine islet cell hyperplasia and may be affected by hCS and kinase activity [47].

placenta GH, which reduce insulin receptor number

Adiponectin is synthesized only in adipocytes

and glucose transport in insulin-sensitive tissues. In

and possibly placenta. Adiponectin expression and

Figure 1.1, the interaction among placental hormone secretion from white adipose tissue decrease with release, maternal metabolic state, and placental func—

advancing gestation [48] and correlate with whole-tion is illustrated.

body insulin sensitivity. Adiponectin acts as an

 endogenous insulin-sensitizing hormone through whereas overexpression of IGF-2 increases placental

receptors on skeletal muscle, where it stimulates

growth. In cultured human trophoblast, both IGF-1

glucose uptake, and liver, where it reduces uptake via

and -2 alter glucose and amino acid transport, and in

adenosine monophosphate-activated protein kinase

sheep, IGF-1 administration alters feto-placental pro—

alpha (AMPK ␣).

tein and carbohydrate transfer and metabolism [60].

Leptin, the product of the LEP gene, was orig—

Placental System A transporter activity is increased in

inally described in the adipocyte and thought to

the placental-specific Igf2 mutant mouse, perhaps as

modulate satiety and energy homeostasis. It is now

a compensatory mechanism, and passive diffusion is

known to be synthesized in other tissues including

reduced [59]. Thus, the promotional effect of IGF-2 on the placenta and to assume other roles. Serum leptin fetal growth may be an indirect one mediated through

concentrations increase throughout human gestation,

the placenta through the IGF type 1 receptor.

beginning to rise in the first trimester and correlating

The level of nutrients appears to regulate IGF con—

with hCG levels. Therefore, leptin alterations are seen

centrations in the fetus because reducing both nutri—

before changes in body weight, suggesting another

ents and oxygen lowers IGF-1, although to a greater

mechanism of regulation [49]. However, serum lep-extent than IGF-2 [61]. Conversely infusion of insulin tin levels correlate to maternal adiposity rather than or glucose increases IGF-1 in the fetus of fasted

placenta mass. Both leptin and leptin receptors are

sheep [34]. Nutritionally sensitive hormones includ-found in syncytiotrophoblast and will stimulate hCG

ing insulin, thyroxine, and glucocorticoids affect IGF

secretion [50].

concentrations in the fetus [62], again with deficiency affecting IGF-1 more than IGF-2. Insulin and IGF-1

levels are positively correlated in the fetus and appear

Placental growth factors

to act synergistically to enhance accumulation of glu—

The placenta is also a major source of growth factors

cose and amino acids in the fetus [62]. Glucocorticoids and their binding

proteins that affect placental and affect both Igf1 and Igf2 gene expression in a tissue—

fetal growth and development. Of these IGF-1 and

specific manner in the fetus [63]. Hence, placental glu-

-2 are the most important mediators of fetal growth.

cocorticoid metabolism may affect fetal growth in a

The Igf1 and Igf2 genes are expressed in many fetal and

gestational specific manner.

placental tissues where the proteins have metabolic,

IGF bioavailability is regulated by expression of

mitogenic, and differentiative actions and may act as

the IGF binding proteins (IGFBP), of which there

local growth regulators [51]. In addition, the IGFs are at least six functionally redundant isoforms, with appear to have a role in trophoblast invasion [52].

IGFBP-1 through -4 being found in humans. Changes

Umbilical levels of IGFs are correlated to birth weight

in IGFBP expression modulate IGF levels and thus

in many species, including humans [53], with IGF-2

fetal growth and are sensitive to nutritional and

concentrations being up to 10-fold higher than IGF—

endocrine regulation [61]. The placenta also expresses 1. Placental IGF-2 mRNA was also positively cor-all the IGFBPs, with IGFBP-1 being predominant.

related with placental weight in a group of normal

They show differential localization, with IGFBP-3

and diabetic pregnancies [54]. Igf2 is an imprinted being found on the microvillous and basal trophoblast gene expressed from the paternal allele in the pla—

membranes and IGFBP-1 predominantly found on the

centa [55] and is expressed in syncytiotrophoblast fetal-facing basal surface [64].

and invasive trophoblast [56]. Deletion of either Igf1

or Igf2 genes results in fetal growth restriction, but

Nutrient partitioning across

deletion of the IGF type 1 receptor gene results in a

more severe growth restriction, suggesting that both

the placenta

IGFs act through the type 1 receptor. Conversely, fetal

Although it is well accepted that maternal nutritional

growth is enhanced by overexpression of IGF-2 or

status, diet, and body size are closely correlated with

deletion of the IGF type 2 clearance receptor [57]. In birth weight, fetal nutrition is clearly not equivalent the mouse, manipulation of the Igf2 gene reduces pla—

to maternal nutrition because the intervening placen—

cental growth by 30% to 40%, involving all cell types in

tal syncytiotrophoblast (ST) constitutes a distinct bar—

Igf2-null mice [58] or just the labyrinthine trophoblast rier between the two circulations. The ST is a syncytial, **6**

in a placenta-specific knockdown of the Igf2 gene [59],

polarized, epithelial cell layer separating the maternal

blood in the intervillous space from the fetal capillary.

by lipase enzymes in the MVM of the placental epithe—

The ST forms by fusion of underlying cytotrophoblast

lium. This liberates free fatty acids for uptake by the

cells and is composed of an apical plasma membrane

epithelial cell. Preferential binding of LCPUFA by a

or microvillous membrane (MVM) facing the mater—

placental-specific fatty acid binding protein (FABP—

nal blood and a basal plasma membrane (BM) toward

pm) allows for specificity of transfer of these crucial

the fetal capillary. The syncytial cell layer thins in

cellular components.

the terminal villous region, and the total transporting

Vectorial transport of calcium to the fetus is

distance at term is 10 microns. This short transport

accomplished by influx of calcium through a variety

distance between the two blood supplies allows for

of channels on the MVM, cytoplasmic binding to cal—

rapid transfer of small hydrophobic molecules and

bindin9K and sequestration in the endoplasmic retic—

blood gases. Larger hydrophilic molecules require spe—

ulum, and, finally, active transport to the fetus by cal—

cialized transporting systems in the epithelial mem—

cium pumps localized exclusively to the basal plasma

branes to provide adequate support for fetal growth.

membrane of the ST.

Fetal blood sampling and the use of stable isotopes

in human pregnancy have allowed for description of

Placental nutrient transport capacity

maternal and fetal nutrient concentrations [65]. These recent advances have established that glucose concen-and fetal growth trations are lower in fetuses and change in parallel to

The placental transport capacity for a number of

maternal levels. Amino acids are significantly higher

important nutrients has been shown to be correlated to

in fetal plasma than their mothers' plasma, with gluta—

birth weight (for review, see Sibley *et al.* [69]). Trans-mate being the only exception. Fatty acids on the whole port capacity for essential amino acids by System L for

are much lower in fetal than in maternal circulation. A

leucine, System y+L for lysine, and System tau for tau—

preferential transfer of essential long-chain polyunsat—

rine and nonessential neutral amino acid transport by

urated fatty acids (LCPUFA) such as docosahexaenoic

System A have been shown to be reduced in cases of

acid (DHA) and arachidonic acid across the placenta

small for gestational age (SGA) and IUGR. Increased

to the fetus [66] ensures adequate supply for brain and amino acid transport capacity in the placenta of large-retinal development.

for-gestational-age (LGA) babies of diabetic mothers

The cellular mechanisms for transport of key

has likewise been reported. In contrast to amino acids,

nutrients across the human placental ST have been

glucose transport capacity appears to be unchanged in

described in detail and recently reviewed [67, 68]. The the placenta of small babies. There are, however, indi-key features can be summarized as follows.

cations that glucose transport capacity is increased in

Glucose is transported across the placenta by facil—

the placenta of LGA babies of diabetic mothers. Mater—

itated diffusion. Abundant expression of the glucose

nal circulating triglycerides are hydrolyzed by lipase

transport protein isoform 1 (GLUT1) on the MVM

enzymes at the microvillous surface of the ST, and sev—
allows for rapid uptake into the ST from the maternal
eral reports indicate alterations in hydrolase enzyme
circulation. A concentration gradient toward the fetus
activity and expression in growth-restricted fetuses
allows for continuous transport to the fetal circulation
and LGA fetuses of diabetic mothers. With respect
and maintains fetal glucose levels that mirror but never
to ion transport, placental calcium pump activity has
exceed those in the maternal compartment.
been shown to be upregulated in both SGA/IUGR and
Active transport allows for fetal accumulation of
LGA babies. Taken together, these data suggest that
amino acids in concentrations considerably higher
specific regulation of placental nutrient transporter
than those found in maternal blood in both mid-and
activity occurs in association with altered fetal growth,
late gestation. The use of the sodium gradient to drive
as shown in Table 1.1 (for review, see Jansson and amino acid transport into the ST on the MVM, fol-Powell [70]).
lowed by passive diffusion out of the cell toward the

Recently, investigations using a nutrient-restricted

fetus, constitutes one important mechanism for amino

pregnant rodent model suggested that reductions in

acid accumulation in the fetal compartment.

placental amino acid transport precede deviations in

Circulating maternal triglycerides (TG) in very

fetal growth [71]. These data have led to the hypothe-low-density lipoproteins (VLDL), as well as both chy-sis that the human placenta may act as a nutrient sen-

lomicrons and TG bound to albumin, are hydrolyzed

sor to coordinate fetal growth with the ability of the

 Table 1.1 Directional changes seen in placental transport compared with term. The placenta in early pregnancy

capacity in pregnancies complicated by altered fetal growth.

responds to insulin by increasing glucose uptake, but

Diabetes + LGA

the term placenta responds to insulin stimulation

IUGR

by increasing amino acid uptake. Other factors that

Transporter

MVM

BM

MVM

BM

indicate an inability of the maternal blood supply to

System A

↓

↔

↔

deliver sufficient nutrients could include oxygen levels,

Leucine

↔

↓

↔

cytokines, and substrates. Although the exact nature

of the nutrient-sensing function of the human pla—

Glucose

↔

↔

↔

centa has not been fully delineated, one intracellu—

Ca 2± ATPase

–

–

lar signaling system may in part account for this type

Na±/H± exchanger

↓

–

↔

–

of regulation. The mTOR controls cell growth by ini—

Na± K± ATPase

↓

↔

↔

↔

tiating or inhibiting protein translation in response

Lipoprotein lipase

↓

–

↑

–

to amino acid availability – in particular, leucine –

through its actions as a phosphatidylinositol kinase–

mother to provide nutrients in individual pregnancies

related kinase. mTOR has been localized to the ST, and

[70]. This would allow for generation of a smaller fetus phosphorylation of downstream mediators of mTOR

when nutrient availability was low and takes advan—

activity is correlated with fetal size. Inhibition of

tage of periods of nutrient abundance by producing

the mTOR system in placental explant cultures by

a larger, potentially more viable fetus. Pathologies in

rapamycin resulted in a reduction in leucine uptake,

fetal growth occur when the maternal supply of nutri—

suggesting a direct link between mTOR and nutrient

ents is severely disrupted, as in cases of shallow pla—

transport to the fetus [72].

cental invasion or long-term famine, or when nutrient

Maternal nutrition and metabolic status in the

supply is chronically in excess, as in maternal diabetes

periconceptual period are critical for successful estab—

and obesity.

lishment of pregnancy. The early-gestation placenta

secretes a number of critical hormones that alter

maternal metabolism and cardiovascular and renal

Regulation of placental nutrient

physiology to allow for maintenance of the pregnancy.

transport

The developing placenta appears to respond to maternal metabolic status, nutrient levels, and/or placental

If the ability of the placenta to transport nutrients is

blood flow to regulate nutrient delivery to the fetus.

regulated in response to the ability of the mother to

These events lead to a careful coordination between

supply those nutrients, then it is logical that mater—

maternal mobilization of nutrient stores, delivery of

nal nutritional signals would be involved in this reg—

those nutrients to the placenta by altering maternal

ulation. IGF-1, insulin, and leptin have been shown

blood flow dynamics, and transport across the pla—

to upregulate placental System A amino acid uptake

cental epithelial barrier to the fetus. The successful

in a variety of experimental systems, suggesting that

integration of these three diverse systems through

maternal markers of adequate nutrition stimulate

maternal/placental/fetal endocrine signaling networks

transport of nutrients to the fetus (for review, see Jones

defines the ultimate pregnancy outcome – a nor-

et al. [68]). Interestingly, the nature of the regula-mally grown, healthy fetus with low risk for adult tion of nutrient transport differs in early pregnancy

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Section 1

Nutritional regulation and requirements for pregnancy and

Chapter

fetal growth

2 **Pregnancyandfeto-placentalgrowth:**

macronutrients

Laura Brown, Tim Regnault, Paul Rozance, James Barry, and William W. Hay Jr.

Introduction

and, in turn, the fetus.

Nutrient substrates for placental and

fetal metabolism

Glucose

The principal metabolic nutrients in the fetus are glucose and amino acids. Glucose is the principal energy

Placental glucose transport and metabolism

substrate for basal metabolism and protein synthe—

Glucose is the primary energy substrate for the mam—

sis and contributes to energy storage in glycogen and

malian fetus and placenta. Normally, the fetus does not

fat. Amino acids provide the building blocks for pro—

produce glucose [5]. Therefore, fetal glucose concen-tein synthesis and growth; they are also oxidative sub-tration is dependent on the placental supply from the strates for energy production, especially when glu—

maternal circulation according to placental facilitated

cose is deficient. Fatty acids are also taken up by the

transport mediated by sodium-independent trans—

fetus; they are primarily used for structural compo—

port proteins. Glucose entry into the fetal circulation

nents of membranes and for fat production in adipose

depends on three steps: (1) uptake from the mater—
tissue. The principal anabolic hormones, insulin and
nal circulation by transporters in the maternal-facing
the insulin-like growth factors (IGFs), are important
microvillous membrane of the trophoblast, (2) trans—
regulators of the synthesis of amino acids into protein,
port across the cytoplasm of the trophoblast, and
cell growth, and cell turnover, but their contributions
(3) transporter-dependent transport across the fetal—
to fetal metabolism and growth are secondary to the
facing basal membrane of the trophoblast into the fetal
supply of nutrient substrates [1–3].
circulation. Glucose transport to the fetus is increased
by placental glucose transporter density, trophoblast
membrane surface area, the maternal-fetal glucose
Growth of the placenta and its
concentration gradient, and uterine and umbilical
blood flows; it is decreased by the thickness of cellular
transport capacity
and interstitial layers between the maternal and fetal
Placental nutrient transfer capacity increases over ges—

vasculature.

tation by increased placental growth, primarily of

At present, only glucose transport proteins 1

membrane surface area, allowing for the increase in

(GLUT1) and 3 (GLUT3) have been found in placen—

nutrient supply required for the growing fetus. Placental tissue locations that would allow for maternal-total size, morphology, and membrane transporter abun—

fetal glucose transport [6]. GLUT1 has been localized dance are regulated by imprinted paternally derived on both maternal-and fetal-facing membranes of the

genes, such as the placental-specific Igf2-H19 gene

synciotrophoblast, whereas GLUT3 has been found on

complex [4]. A larger paternal versus maternal Igf2

maternal facing microvillous membranes of the tro—

gene allele supply leads to a larger placenta and the

phoblast. In the trophoblast, GLUT1 protein concen—

potential for a larger fetus. Activity of the imprinted

trations are threefold higher in the maternal-facing

genes can also be affected by epigenetic modification,

membranes than in the fetal-facing membranes. In

which allows for considerable environmental influ—

vitro dual cotyledon perfusion studies have demon—

ence over gene expression. Thus, DNA methylation can

strated a twofold greater uptake of glucose from

12

limit placental-specific Igf2 gene activity, leading to

the maternal than the fetal vasculature [7]. These **Chapter 2: Pregnancy and feto-placental growth: macronutrients** functional data are supported by placental studies 2. The placenta is a highly metabolically active

showing a sixfold greater maternal-facing trophoblast

organ. Its significant nutrient requirements are

membrane surface area and a threefold higher GLUT1

necessary to increase its growth, metabolism,

concentration compared with the fetal-facing basal

and transport capacity to support the increasing

membrane [8, 9]. This unique arrangement of trans-metabolic needs of the growing fetus as gestation porters allows for the high rate of glucose transport

advances.

from maternal to fetal plasma, which is directly related

3. Glucose transport to the fetus is increased by tro—

to the maternal plasma glucose concentration and the

phoblast membrane surface area, the maternal—

maternal-to-fetal plasma glucose concentration gradi—

fetal glucose concentration gradient, and uterine

ent [10]. In contrast, uteroplacental glucose consump-and umbilical blood flows but is decreased by the tion is regulated by fetal glucose concentrations [11].

thickness of cellular and interstitial layers between

Thus, when fetal plasma glucose concentrations are

the maternal and fetal vasculature.

relatively higher, glucose is shunted toward placental

4. When fetal plasma glucose concentrations are rel—

consumption. Conversely, if fetal plasma glucose con—

atively higher, glucose is shunted toward placental

consumption. Conversely, if fetal plasma glucose

centrations are relatively lower, glucose transport into

concentrations are relatively lower, glucose trans—

the fetal circulation increases, but placental glucose

port into the fetal circulation increases, and placen—

consumption diminishes. This unique reciprocal relatal glucose consumption diminishes.

tionship regulates fetal and placental glucose utiliza—

5. From mid-gestation to term, fetal glucose demand

tion in relation to maternal glucose concentration.

increases 14-fold.

From mid-gestation to term, fetal glucose demand

increases 14-fold [1]. To meet this higher fetal glucose demand, placental-to-

fetal glucose transfer increases through two discrete developmental changes. First,

Fetal glucose utilization

the maternal-to-fetal glucose concentration gradient

The fetus metabolizes glucose in several ways, includ—

increases as the fetal glucose concentration decreases

ing oxidation for energy requirements (55% of total

in relation to maternal plasma glucose concentrations

glucose utilization) and as a carbon source for pro-

[12]. The decrease in fetal glucose concentration is the duction of various macromolecules, such as glycogen, result of increased glucose utilization in the placenta

glycolytic products (e.g. lactate, riboses, and glycerol),

and the fetus. Near term, in vivo and in vitro stud—

proteins, and fatty acids. The fraction of fetal oxygen

ies have shown that as much as 60% to 80% of glu—

consumption provided by glucose oxidation is approx—

cose taken up by the placenta is not transferred to

imately 30%, with most of the remainder provided by

the fetus but is instead consumed by the placenta [11,

lactate and, to a lesser extent, amino acids [10, 14]. In 12], thereby lowering the concentration of glucose in humans the estimated fetal glucose utilization rate in the uterine and umbilical veins. Increased fetal glucose

late gestation is 5 to 6 mg/kg/min [15]. This is simi-utilization occurs in response to increased fetal insulin lar to the rate determined in large animal models near

production and growth of fetal insulin-sensitive tis—

term [1, 2] and corresponds to glucose utilization rates sues (primarily skeletal muscle). Quantitatively more in human newborn infants. Fetal glucose utilization

important, placental glucose transport capacity also

rates normalized to fetal weight decrease from mid-to

increases significantly as a function of the increase

late gestation as a result of the growth of organs, such

in placental trophoblast surface area and its directly

as muscle, bone, and adipose tissue, which have lower

related increase in glucose transporter abundance

rates of glucose utilization.

[8, 13].

Acutely, the rate of fetal glucose utilization is regulated by maternal plasma glucose concentration and

placental glucose transport to the fetus. This regula-

Physiological and clinical points for placental tion is partly due to fetal insulin secretion. Increased

glucose and metabolism

placental transport of glucose to the fetus increases

1. Glucose is the primary energy substrate for the

glucose concentrations, which stimulate fetal insulin

mammalian fetus and placenta.

secretion. Insulin then acts to increase fetal glucose

utilization and lower glucose concentrations [10].

 In addition, glucose and insulin clamp experiments Fetal glucose production

in fetal sheep, in which glucose is infused to pro—

Although fetal glucose production has not been

duce desired concentrations and increases in insulin

demonstrated in humans [5], glucose production from concentration are blocked by simultaneous infusions glycogenolysis and gluconeogenesis has been demon—

of somatostatin, have demonstrated that fetal glu—

strated under certain conditions in laboratory ani—

cose concentrations regulate glucose utilization inde—

mals. Glycogen is normally produced in the fetal liver

pendently of fetal insulin concentrations. Despite the

from glucose, although lactate and certain amino acids

changes in overall glucose utilization, the fraction

also can act as precursors. Hepatic glycogen content

of glucose oxidized in these short-term studies is

normally increases during the later part of gestation.

unchanged (approximately 55% in fetal sheep) [14].

Following experimental manipulation, the fetal liver

Therefore, in the acute setting, fetal glucose utilization

can acutely produce glucose from glycogen, a pro—

is regulated by acute changes in fetal insulin and glu—

cess that is rapidly activated by pharmacologic con—

cose concentrations.

centrations of catecholamines and glucagon, as well

as by hypoxia (which probably acts by increasing catecholamine secretion). Sustained glucose production

Physiological and clinical points for fetal glucose utilization

by the fetal liver occurs under experimental conditions through gluconeogenesis – for example, in cer—

1. Fetal glucose concentration is dependent on

the placental supply through facilitated trans—

tain models of IUGR or sustained fetal hypoglycemia

port mediated by sodium-independent transport

[17, 18] – and sustained glucose production, though of proteins.

modest degree, does develop naturally in late-gestation

2. From mid-gestation to term, fetal glucose uti—

fetal sheep. Functional activities of the hepatic gluco—

lization increases 14-fold, which is met by an
neogenic pathway are usually present late in fetal life,
increase in the maternal-to-fetal glucose concen—
following stimulation by the late-gestation increase in
tration gradient and in the placental trophoblast
fetal cortisol secretion.
surface area and glucose transporter abundance.
However, fetal glucose utilization rates normal—

Intrauterine growth restriction

ized to fetal weight decrease from mid-to late
gestation.
IUGR is characterized by fetal hypoglycemia and
3. Late in gestation the estimated fetal glucose uti—
hypoinsulinemia and serves as an example of how the
lization rate in late gestation is 5 to 6 mg/kg/min.
placenta and fetus adapt to such chronic changes to
4. Fetal glucose utilization is regulated by acute
maintain normal glucose metabolic rates. On an abso—
changes in fetal insulin and glucose concentra—
lute basis, placental glucose transport is reduced by
tions.

65% at near term in IUGR gestations, but on a relative

weight basis, it is similar to control transport rates [19].

Many studies have confirmed, in fact, that the severity of the fetal growth restriction and placental insufficiency may affect the degree and causal mechanisms

Fetal insulin secretion

of fetal hypoglycemia.

Insulin is secreted by the -cell, located in the islets of

Several animal models of IUGR or experimental

Langerhans within the pancreas, which develops dur—

fetal hypoglycemia have shown that weight-specific

ing the first trimester. Data from fetal sheep indicate

fetal glucose utilization rates are not severely decreased

that baseline insulin concentrations and the capac—

from control rates [14, 19]. Recent data from these ity for insulin secretion increase from mid-gestation models have shown maintained or increased insulin

toward term, although this secretory capacity is signif—

sensitivity as a mechanism that maintains the glu—

icantly less than in neonatal animals [14]. In humans cose utilization rates. This is consistent with data glucose-stimulated insulin secretion has been demon—

in human IUGR infants obtained within the first

strated in the mid third trimester, although function—

48 hours of life showing increased insulin sensitivity

ing islets are present, as in the sheep, by mid second

[20]. Increased insulin sensitivity for glucose utiliza-trimester [16].

tion is required to maintain normal glucose utilization

 rates because another adaptation of the severely IUGR

Amino acids

fetus is decreased baseline and glucose stimulated

insulin concentrations, probably due to decreased

Protein (nitrogen) requirements

numbers of pancreatic -cells [16, 21]. Again, a wide variety of many animal models of IUGR and selec-during pregnancy tive fetal hypoglycemia also show decreased insulin

Current dietary recommendations for increased pro—

concentrations, decreased glucose stimulated insulin

tein intake during pregnancy are based on estimates

secretion, and decreased abundance of pancreatic -

of overall accumulation of nitrogen in the concep—

cells in the resulting smaller islets [14, 22].

tus. Total nitrogen concentration measurements have

If fetal adaptations to IUGR, such as increased

been used to estimate the rate of protein accretion

insulin sensitivity despite decreased insulin secretion

in tissues, because most of the total nitrogen is rep—

and -cell mass, persist into postnatal life and into

resented by amino acid nitrogen uptake [3]. Several late childhood and adulthood, they could underlie methods have been used to estimate total nitrogen

the increased risk that IUGR infants have of devel—

accretion during pregnancy. Measurements of total

oping obesity and Type II diabetes mellitus as adults.

body potassium, which estimate lean body mass, pre—

Increased insulin sensitivity might predispose the for—

dict an additional nitrogen accretion of 90 g (550 g

merly IUGR infant to have abnormally increased rates

protein, N × 6.25) during pregnancy from increased

of fatty acid deposition, leading to obesity and even—

protein deposition in the placenta, fetus, uterus, red

tually insulin resistance. If a -cell defect persists

blood cells, plasma, and other maternal tissues. Nitro—

that limits the insulin response to peripheral insulin

gen balance studies in pregnant women consistently

resistance, then Type II diabetes mellitus would fol—

show an increase in nitrogen retention as pregnancy

low. This problem raises two important areas for

progresses and estimate nitrogen deposition to be

future research. One area is in the prenatal treatment

approximately 1.2 to 1.8 g of nitrogen/day by the third

of IUGR. Previous human studies using nutritional

trimester of pregnancy [23]. Because the fetus con-interventions have demonstrated variable results with tributes most to nitrogen requirements, both anthro—

potential fetal toxicity. However, mechanisms of fetal

pometric measurements and postmortem chemical

toxicity are unknown, and large animal models are

composition studies of infants born at different ges—

particularly useful for determining these mechanisms

tational ages have predicted fetal protein accretion to

and investigating safe interventions for established

be 64 g nitrogen (400 g protein) at term [24]. Nonfat IUGR. In addition, future research is needed to deter-dry weight and nitrogen content are linearly related to mine whether postnatal feeding practices should be

fetal weight; the rate of fetal growth, therefore, deter—

modified in the previously IUGR infant during the

mines the macronutrient requirements for fetal pro—

period of increased insulin sensitivity with the goal

tein accretion gain. On the basis of such information,

of preventing future insulin resistance and obesity

6 to 10 g of protein per day is generally recommended

without sacrificing long-term neurodevelopmental

for pregnant women.

outcomes.

Fetal and placental amino acid requirements for

net protein accretion, however, do not appear to

Physiological and clinical points for intrauterine depend only or directly on maternal diet. A posi-

growth restriction

tive correlation between fetal weight and maternal

1. IUGR is characterized by fetal hypoglycemia as well

protein intake has not been demonstrated. It also

as by hypoinsulinemia and adaptations that main—

has been shown that when pregnant women receive

tain normal glucose metabolic rates.

high protein supplementation, there is a significantly

2. On an absolute basis, placental glucose transport

increased risk of small-for-gestational-age birth [25].

is reduced by 65% near term in IUGR gestations,

Furthermore, stable isotope studies performed during

but on a relative weight basis, it is similar to con—

pregnancy indicate that lower rates of urea synthesis

trol transport rates.

(reflecting decreased amino acid oxidation) and lower

3. Recent data from animal models have shown main—

rates of branch chain amino acid transamination func—

tained or increased insulin sensitivity as a mecha—

tion to conserve nitrogen accretion for both maternism that maintains the glucose utilization rates in

nal and fetal requirements [26]. Therefore, changes in IUGR.

15

maternal protein metabolism independent of protein

Section 1: Nutritional regulation and requirements for pregnancy and fetal growth intake contribute significantly to protein delivery to ferred amino acids (reviewed in Regnault *et al.* [28]).

the fetus. Increased maternal lean body mass also may

Not only amino acids are transported from the mater—

positively affect protein turnover and fetal growth [26].

nal circulation to the fetus, they are also transported

With contributions from diet, maternal body compo—

from the fetus to the placenta, so the net uptake a

sition, and maternal protein turnover, protein delivery

fetus receives is the sum of these movements. Amino
to the growing fetus ultimately depends on umbilical
acids supplied to the placenta from the maternal and
amino acid uptake from the placenta and the ability to
fetal circulations are metabolized for energy produc—
transport amino acids from the maternal to the fetal
tion and amino acid synthesis.
circulation.
As pregnancy advances, placental amino acid
transport capacity must increase to meet the nutrient
Placental transport of amino acids from
demands of the developing fetus. Factors that change
with advancing gestation to affect the total placen—
mother to fetus
tal transport of amino acids include uteroplacental
The net uptake of amino acids by umbilical circulation
blood flow, trophoblast villous surface area, compe—
through the placenta represents the dietary supply of
tition among amino acids for the same transporter,
amino acids for fetal growth and protein metabolism.
placental metabolism of amino acids, and transport

In fetal sheep at term, total fetal umbilical nitrogen

system location and activity. Therefore, these changes

uptake is 0.91 g nitrogen/kg/day, similar to the cal—

associated with advancing gestational age, in conjunc—

culated total fetal nitrogen requirement of approxi—

tion with maternal diet and metabolic condition, alter

mately 1 g nitrogen/kg/day based on nitrogen accre—

amino acid transport and fetal growth potential. The

tion data and estimated fetal urea production rates

nutritional requirements for amino acids are highest

[27]. The net uptake of most amino acids exceeds during mid-gestation because of high fractional pro-their net accretion by considerable amounts, indicat-tein synthetic and growth rates during this time [29].

ing that the fetus must oxidize the balance not used

It is important to note that placental transport rates

for net protein accretion. As in postnatal life, sev—

of amino acids are not significantly affected by moderal amino acids (primarily the branch chain amino

erate fluctuations in uterine or placental blood flow,

acids leucine, isoleucine, and valine, as well as lysine)

because they are actively transported and thus clear—

cannot be synthesized in the fetus. Thus, limitation

ance is diffusion limited. However, during the second

of supply of these essential or indispensable amino

half of gestation, increasing placental surface area falls

acids is likely to lead to reduced fetal protein accre—

short of the increase in fetal size [8]. Therefore, increas-tion and growth. For the nonessential amino acids, ing amino acid transporter abundance and activity,

fetal requirements can be met by production within

in combination with villous surface area, appear nec—

fetal tissues. The placenta also contributes to fetal

essary to support fetal growth, and both have been

amino acid and nitrogen balance through placental—

shown to increase over gestation [30].

fetal amino acid cycling. In other words, certain amino

acids (e.g. glutamine and glycine and their metabolic

products glutamate and serine) are produced in the

Fetal amino acid metabolism

placenta, metabolized in the placenta, or taken up from

Accretion of amino acids is an essential component

the fetal pool to optimize metabolic processes such as

of fetal protein synthesis and growth. In the grow—

signaling of protein synthesis and oxidation for energy

ing fetus, net protein synthesis exceeds net protein production [28].

degradation, yielding net protein accretion, although

Amino acids are transported across the placental

both processes continue simultaneously. Direct mea—

trophoblast by energy-dependent amino acid trans—

surements of fetal protein synthesis, breakdown, and

porter systems. Because the concentration of most

oxidation have been made with carbon-labeled iso—

amino acids is higher in the fetal than the maternal

topic tracers of selected amino acids. A net uptake of

plasma, transport usually occurs actively against a con—

amino acids by the fetus in excess of accretion require—

centration gradient. Amino acid transport systems are

ments for growth implies that this excess portion of

present on both the maternal-facing (apical) and fetal—

amino acid uptake is used for oxidation, and sev—

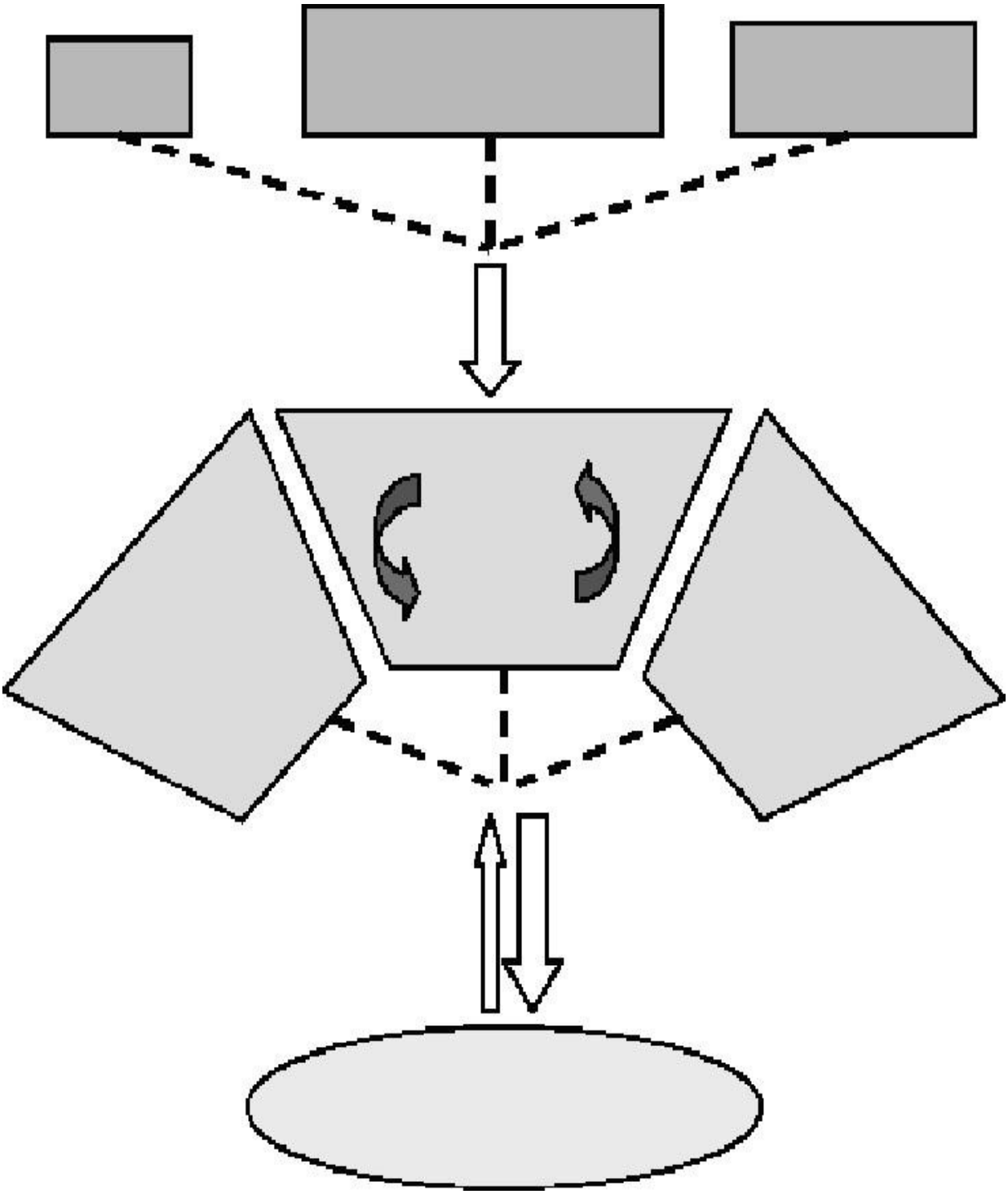
facing (basal) surfaces of the trophoblast in the human

eral tracer studies have documented 14CO

2 production

placenta. Each system transports a collection of pre—

from amino acid oxidation [3].



and insulin-like growth factor 1 (IGF-1) **MATERNAL**

are important growth hormones for the fetus and

Adaptations in

Body

promote the utilization of substrates such as amino

Diet

protein turnover

composition

acids in fetal life. In vivo studies in the ovine fetus

have demonstrated that both hormones increase cellular amino acid uptake, promoting their direct syn-

MATERNAL AA SUPPLY

thesis both into protein and into oxidative metabolism

PLACENTAL

and energy production [31, 32]. Insulin and IGF-1

Placental

regulate translation initiation and protein synthesis

AA cycling

through well-recognized intermediates in their sig-

Gestational

AA

Fetal

age-related

nal transduction pathways, including mitogen acti-

transporter

functions

abundance/activity

vated pathway (MAP) kinase and mammalian target

(e.g. surface)

area)

of rapamycin (mTOR) [33, 34]. In mammals, mTOR

functions as a sensor for growth factors, nutrients,

FETAL

energy, and stress and coordinates these signals to reg-

NET FETAL AA SUPPLY

ulate cell growth and proliferation. Amino acids also

have been documented to function as direct-acting

AA uptake – AA oxidation =

nutrient signals that activate mRNA translation initia-

Fetal protein accretion

tion via mTOR. Leucine has been documented as the

major regulator of this pathway, as well as an impor—

Figure 2.1 Schematic diagram showing maternal, placental, and

fetal influences on fetal protein accretion and growth.

tant regulator of gene expression during cellular stress

[35].

surface area has been reported for the IUGR placenta,

indicating that morphometric changes also contribute

Abnormal delivery of amino acids to the

to overall reduction in placental amino acid transport capacity in cases of IUGR [38]. Further investi-fetus with IUGR

gation into mechanisms involved in the development

Amino acid and protein insufficiency produces growth

of IUGR in relation to amino acid uptake and utiliza—

failure of the whole fetus and preterm infant. Pla—

tion in fetal life is critical because of the short-and

cental amino acid transport studies in both humans

long-term consequences for neonates born with this

and sheep have consistently found reduced placental

condition, including increased morbidity and mortal—

transport of amino acids, and in particular leucine,

ity in the neonatal period as well as the predisposition

across the IUGR placenta [3, 36]. Furthermore, in vitro to abnormal muscle development, peripheral insulin studies on isolated human syncytiotrophoblast

plasma

resistance, obesity, diabetes, and cardiovascular dis—

membranes have demonstrated reduced expression,

ease later in life [39].

activity, or both in several specific amino acid transport systems on both the maternal-and fetal-facing

Physiological and clinical points for placental and plasma membranes of the trophoblast from IUGR

fetal amino acid metabolism

pregnancies [37]. Although reduced placental trans-1. Placental and fetal requirements for protein accre-port of selected or all amino acids might be expected tion during pregnancy are met by adaptations in

from such IUGR placentas and thus contribute to

maternal protein turnover and, to a lesser degree,

lower fetal plasma amino acid concentrations dur—

maternal protein intake.

ing mid-gestation and term, other IUGR studies

2. Amino acids are transported from mother to fetus

have reported maintenance of circulating fetal con—

across the placental trophoblast against a concentration gradient by energy-dependent amino acid

centrations [37]. Many factors contribute to fetal transporter systems.

plasma amino acid concentrations in utero, such

3. Amino acid transporter abundance and activity

as amino acid supply and the balance of rates of

and villous surface area increase during the second

fetal protein synthesis, breakdown, and catabolism

half of gestation to support fetal growth.

(Fig. 2.1). Thus, reliance on fetal plasma concentration 4. Placental insufficiency will result in intrauterine data alone in assessing the transport capacity of a pla—

fetal growth restriction, in part as a result of

centa may not be entirely accurate. Reduced placental

 gestation, with increased adipose tissue lipolysis and reduced placental surface area, reduced expres—

reduced uptake of circulating triglycerides as adi—

sion and/or activity of amino acid transporters, as

pose tissue lipoprotein lipase activity decreases. The

well as decreased flux of amino acids across the

placenta.

maternal liver also overproduces triglycerides under

these conditions, and the maternal intestine increases

its absorption of dietary lipids, particularly in late

Lipids

gestation. These changes in maternal lipid metabolism
produce increasing concentrations of nearly all types
Placental lipid metabolism and fetal
of circulating plasma lipids, including free fatty
acids, glycerol, and triglyceride-rich very low-density
lipid supply
lipoproteins (VLDLs) and chylomicron particles.
The transport of fatty acids and other lipid substances
Maternal plasma concentrations of keto acids (-
across the placenta and the deposition of lipids in fetal
hydroxybutyrate and acetoacetate) increase rapidly
adipose tissue are primarily late-gestation phenomena.
during fasting and can contribute significantly to the
Essential fatty acid transport, however, begins early
supply of lipid substrates to the placenta and fetus [2].
in gestation, allowing membrane lipids, particularly
those of neurons and glial cells, to develop throughout
Placental uptake, synthesis, and
gestation.
Fetal uptake and plasma concentrations of all fatty
metabolism of fatty acids

acids and structural lipids correlate directly with the

After entering the placenta, fatty acids can be used for

fatty acid/lipid composition of the maternal plasma

triglyceride synthesis, cholesterol esterification, mem—

and, therefore, indirectly with maternal diet, metabolic

brane biosynthesis, direct transfer to the fetus, or oxi—

conditions (fed vs. fasting), and disease states (e.g. dia—

dation [42]. Placental tissue from different species betes). Experimentally, diabetic animal models and expresses lipoprotein lipase activity as well as phos—

those fed oil-rich diets produce fetuses and newborns

pholipase A2 [43]. Maternal plasma triglycerides are at term gestation that have increased whole-body adi-hydrolyzed by these enzymes, and the fatty acids pose tissue and fat stores as well as organ (particu—

that are released are then taken up by the placenta.

larly liver) lipid contents [40]. Quantitatively in preg-In the trophoblast cells, the fatty acids are then re-nant women, the net flux of free fatty acids (FFAs) into esterified and further hydrolyzed, facilitating their dif—

the fetus from the maternal circulation can account

fusion into fetal circulation. Most of these processes

for 50% to 100% of the fetal requirement of fatty acids

increase in late gestation and recent gene expression

during the end of pregnancy, although lipid synthe—

patterns show upregulation of the genes responsible

sis in the fetus from glucose and FFAs does contribute for placental lipid metabolism and transport early dur— significant amounts of fat in late gestation. Overall, ing this period. Normally, increased maternal lipol— there is a general relationship between the permeabil— ysis during pregnancy provides substrate for mater— ity of the placenta to lipids, especially fatty acids, and nal energy metabolism, which spares glucose for the the adiposity of the fetus at term. Among mammals, fetus and also increases maternal plasma FFA con— human fetuses develop the most fat, 15% to 18% of centrations. Furthermore, placental triglyceride con— body weight at term, compared with other mammals tent increases in women who are fasting, who deliver in which fetal fat content at term is 3% or less of body preterm infants, or who have diabetes mellitus – all weight [2].

conditions in which maternal plasma free fatty acid Direct placental FFA uptake and transfer to the concentrations are increased. In contrast, lipolysis is fetus increases over gestation by increased placen—

lower in pregnancies complicated by IUGR, in which

tal lipoprotein lipase activity, which appears to be

both placenta and fetus have reduced lipid concentra—

increased by glucose and insulin and expression and

tions and fat mass [44].

activity of the fatty acid transporter binding protein

Fatty acid transport into the fetal circulation is pri—

L-FAB [41]. These processes contribute to the greater marily determined by the transplacental gradient of lipid transport to the fetus and fetal macroscomia

FFAs and the fetal plasma concentrations and bind-

(obesity) common in gestational diabetics. Maternal

ing site availabilities of fatty acid binding proteins in

lipid metabolism changes to a catabolic state in late

the fetal circulation; normal conditions generally favor

 maternal-to-fetal transport. All fatty acids cross lipid parallels those for maternal and fetal (or neonatal)

bilayers, such as those in the syncytiotrophoblast, by

concentrations of LCPUFAs and other essential fatty

rapid simple diffusion. In addition, fatty acid transport

acids such as DHA in healthy women eating normal,

across membranes is facilitated by fatty acid binding

unsupplemented diets and after fish oil supplementa—

proteins (FABPs), which aid in intracellular channel—

tion during pregnancy [49]. In fact, because the devel-ing of fatty acids [45].

oping fetus depends primarily on the maternal supply

Another major effect of maternal fatty acids taken

of essential fatty acids and AA status in preterm infants

up by the placenta involves their role as signals

has also been correlated with birth weight, maternal

for additional metabolism in the placenta and fetus

dietary supplementation with LCPUFA-rich oils dur-

[46]. For example, the nuclear receptor peroxisome ing the last trimester of pregnancy to increase lev-proliferator-activated receptor gamma (PPAR gamma) els in fetus has been advised. However, foods conis expressed in placental trophoblast cells and is essen—

taining lipid peroxides are potentially toxic, and the

tial for placental development, trophoblast invasion,

higher the content of LCPUFAs in the diet, the more

differentiation of cytotrophoblasts into syncytium, and

likely that peroxidation will occur, because excess

regulation of fat accumulation in trophoblasts, and

intake of PUFAs could reduce antioxidant capacity

even produce fetal membrane signals that lead to par—
and enhance susceptibility to oxidative damage. Fur—
turition. Low-density lipoprotein cholesterol is also
thermore, experimental animal studies have shown
taken up by endocytosis into trophoblast cells; it is
improvements in fetal and neonatal growth rates
the major precursor for placental production of pro—
and neurodevelopmental indices with maternal -
gesterone and estrogen. Some of this cholesterol is
linolenic acid supplementation, in agreement with pre—
transferred directly to the fetus, although most of fetal
vious observations in humans fed diets rich in AA
cholesterol is synthesized in the fetal liver.
in which the proportion of linolenic acid in plasma
phospholipids was decreased, likely as a consequence
Essential fatty acid metabolism and transfer
of replacing linolenic acid with AA in tissues [50].
Furthermore, although n-3 LCPUFA supplementation
by the placenta
during human pregnancy does enhance pregnancy
The supply of essential, long-chain polyunsaturated

duration and fetal head circumference at term ges—
fatty acids (LCPUFAs: linoleic acid or 18:2 omega-6,
tation, the mean effect size is small, making it dif—
and ␣-linolenic acid or 18:3 omega-3) is critical to
ficult to determine the implications for later growth
the synthesis of structural lipids. All of the omega-6
and development. Therefore, because the benefits and
and omega-3 fatty acid structures acquired by the fetus
risks of modifying maternal fat intake in pregnancy
must come from the mother via the placenta, either
and lactation are not yet completely established and the
in the form of these two essential fatty acids or their
safety of high intakes of LCPUFAs during pregnancy is
principal LCPUFA derivatives, arachidonic acid (AA,
still unclear, further studies are required before defini—
20:4 omega-6) and docosahexaenoic acid (DHA, 22:6
tive recommendations to markedly increase LCPUFA
omega-3) [47].
intake in pregnancy can be made.
Essential fatty acids are not synthesized in the pla—
This point, however, must be considered in light

centa, even though concentrations of the EFAs are

of data showing that pregnant women in some coun—

higher in the fetus than in the mother [48]. Although

tries, particularly the United States, have remark—

these results indicate that fetal AA acid and DHA are

ably lower LCPUFA concentrations, and their key

transferred directly from the mother to a higher bind—

metabolic derivatives than found in other populations,

ing capacity in the fetal plasma, they do not exclude

such as in Scandinavia, where natural dietary fish oil

the possibility that some might be synthesized from

intake is relatively higher. More recent studies are now

linoleic and linolenic acids in the fetal liver.

showing potentially important and statistically significant benefit to the offspring of pregnant mothers supplemented with dietary oils that increase DHA and

Maternal diet and essential fatty acid supply

related essential fatty acids in the fetus. For example,

In general, there is a direct correlation between mater—

children who were born to mothers who had taken

nal essential fatty acid nutrition and neonatal growth

cod liver oil, rich in DHA, AA, and eicosapentaenoic

and head circumference in humans; this correlation

acid, during pregnancy and lactation scored higher on

mental processing tests at age 4 years compared with Fatty acid oxidation in the fetus

children whose mothers had taken corn oil [51]. Thus, There is little evidence for much fatty acid oxidation maternal intake of very long-chain n-3 PUFAs durin the fetus. RNA expression and activity of long—

ing pregnancy and lactation may be favorable for later

chain fatty acid oxidation enzymes are low in fetal

mental development of children.

tissues, although they subsequently increase rapidly

after birth, even in preterm infants. The abundant glu—

Fetal accumulation of essential fatty acids

cose supply to the fetus also limits fatty acid oxida—

Production of AA acid and DHA from essential fatty

tion by producing high concentrations of malonyl—

acid precursors occurs in term and preterm infants,

CoA, which inhibits carnitine palmitoyl transferase

but it is not clear whether the fetus is capable of

1 (CPT1) activity, the rate-limiting enzyme for long—

fatty acid desaturation and elongation [52]. Both AA chain fatty acid entry into

mitochondria that already and DHA are readily incorporated into the structural

is low in fetal tissues.

lipids of the developing brain, where, besides their

role in maintaining membrane fluidity, permeabil-

Physiological and clinical points for placental and ity, and conformation, they play an important func-

fetal lipid metabolism

tional role. For example, once released from phos—

1. Human fetuses are unique among land mammals

pholipids by the action of phospholipase A2, AA is

in the large amount of “white” fat that they accu—

the main precursor for eicosanoids, prostaglandins,

mulate over the last trimester of pregnancy – 12%

and leukotrienes and is essential for fetal and neona—

to 18% of body weight.

tal growth [53]. DHA has a key role in the develop-2. Placental and fetal lipid uptake and fetal plasma ment of visual function. Depletion of DHA from the

lipid concentrations are directly related to mater—

retina and brain results in reduced visual function and

nal plasma lipid concentrations and thus to maternal diet.

learning deficits, emphasizing the critical roles of DHA

3. Placental lipid transfer occurs directly for FFAs and

in membrane-dependent signaling pathways and neu—

indirectly by active metabolism for many other

rotransmitter metabolism. Increasing evidence from

lipid products.

human studies of maternal n-3 fatty acid supplementa—

4. Essential fatty acids are transported by specific

tion during pregnancy does indicates beneficial effects

transporters over the bulk of gestation.

on visual function of the offspring, but primarily in

5. Fetal and neonatal neurological development is

infants born preterm; similar results relate to mater—

positively affected by EFA supply.

nal n-3 intake during pregnancy and infant neurode—

6. Most of fetal lipid uptake and production is used

velopmental outcome [54]. Specificity of most of the for fat production in adipose tissue and not for beneficial effects, however, is confounded by improved

oxidation.

postnatal n-3 dietary intake of the preterm infants.

Fetal lipid metabolism

Acknowledgments

The fetus also develops its own mechanisms that

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enhance lipid uptake, including insulin secretion that increases fatty acid utilization (largely to develop adipose tissue) [1]. Such increased fetal lipid metabolism also lowers fetal plasma fatty acid concentrations relative to those in the maternal plasma and thereby increases the maternal-to-fetal fatty acid concentration gradient and the diffusion of fatty acids into the fetal plasma. Increased fetal albumin synthesis and plasma concentrations directly increase the transfer of fatty acids across the placenta by providing increased esterification capacity in the fetal plasma.

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23

Section 1

Nutritional regulation and requirements for pregnancy and

Chapter

fetal growth

3**Mineralrequirementsofthemother**

and conceptus

Lorraine Gambling and Harry J. McArdle

Introduction

roles, discussing how the symptoms of deficiency over-

lap, and what the short-and long-term consequences

During development, the fetus is entirely dependent

may be. For convenience, we have arranged the para—

on the mother for the supply of minerals. Although

graphs on their physiological roles alphabetically, but
the dietary level required is relatively small, they are
this should not be taken as an indication of their rela—
essential because they play central roles in all stages
tive importance to normal growth and development.
of growth and development. Minerals are both central
Calcium is the most abundant mineral in the
components of catalytic sites and stabilizing factors
human body. More than 99% of total body calcium is
in many enzymes and transcription factors. Therefore,
stored in the bones and teeth, where it functions to
they play a role in almost every cellular function, from
support their structure. The remaining 1% is found
protein translation to intracellular signalling. Clearly,
throughout the body in blood, muscle, and intersti—
any limitation in the supply will have profound effects,
tial fluids [3]. Calcium also has an important regu—
both short-and long-term, for the mother, fetus, and
latory role. The 1000-fold gradient between extracel—
newborn. For the fetus, these damaging effects can
lular and intracellular ionic calcium concentration is

become apparent before, or even in the absence of, any fundamental to cellular signal transduction and ampli— clinical signs of deficiency in the mother. The range fication. An induced influx of calcium triggers and and extent of the detrimental effects seen in the devel— activates a variety of cellular physical and metabolic oping fetus are dependent on the severity of the defi— events, including muscle contraction, neurotransmis— ciency, whether it occurs only for a single mineral, sion, enzyme and hormone secretion, and muscle and and the gestational age at which the deficiency occurs. blood vessel contraction and relaxation [4].

Mineral supplementation during pregnancy is com— Copper can act as an electron acceptor or donor. monplace, but supplementation late in gestation or in As such, it is central to many redox-active enzymes. postnatal life may not overcome the damage caused by For example, it is a central component of many the earlier restriction.

enzymes involved in metabolic reactions including angiogenesis and oxygen transport [5]. Synthesis of a **Minerals essential for**

pregnancy range of essential compounds, such as neurotransmit—

Because of the difficulties, both ethical and practical,

ters and the proteins of connective tissue, is depen—

of studying the effect of maternal mineral status in

dent on copper-containing enzymes, lysyl oxidase and

humans, our current level of understanding has been

dopamine -monooxygenase, respectively. It is a cen—

derived mainly from observational and intervention

tral part of the cytochrome complexes involved in

studies in which maternal intakes, low or high, are

energy metabolism.

associated with adverse or favorable pregnancy out—

Iodine is a nonmetallic trace element; approxi—

comes [1] and from extrapolation from animal studies mately 75% of the body's iodine is located in the thy-

[2].

roid gland. The only role known for iodine in the

Minerals known to be of major importance during

human body is in the synthesis of thyroid hormones by

pregnancy include calcium, copper, iodine, iron, mag—

the thyroid gland, and all biological actions of iodine

nesium, selenium, and zinc. Deficiencies in these min—

are ascribed to the thyroid hormones. The major thy—

erals have been associated with complications of preg—

roid hormone secreted by the thyroid gland is thyrox—

nancy, childbirth, or fetal development. In this review,

ine, which is taken up by cells and converted into tri-

we consider each, briefly examining their physiological

iodithyrone. These two enzymes are required for the

 maintenance of metabolic rate, cellular metabolism,

teins that contain zinc fingers [9]. This role for zinc and integrity of connective tissue [6].

ensures that it is vital for successful RNA synthesis and

Almost two thirds of iron in the body is found in

hormone responses.

the red blood cells as hemoglobin, the protein that carries oxygen to tissues. Myoglobin, the oxygen reserve

Mineral deficiencies

in muscle, amounts to approximately 10% of the

Mineral deficiencies are a global problem, affecting

body iron. The remaining iron is ubiquitously present

both the developed and developing worlds [10]. Pop-throughout the body. There are four major classes of ulations significantly at risk are the elderly, infants,

iron-containing proteins: hem proteins, iron-sulphur

growing children, and pregnant women. It is clear that

proteins, iron storage and transport proteins, and iron—

a deficiency in one or more of these essential miner—

containing enzymes. Iron is an integral part of sev—

als will affect all major physiological functions because

eral classes of enzymes, including cytochromes, the

these deficiencies will result in alteration in cell divi—

role of which in oxidative metabolism is to trans—

sion, cellular differentiation, and the normal pattern of

fer energy within the mitochondria. Other iron—

protein synthesis. Years of medical and scientific stud—

containing enzymes are involved in the synthesis of

ies have shown the significant and far-reaching con—

steroid hormones and of bile acids, detoxification of

sequences of mineral deficiencies on the population,

foreign substances in the liver, and synthesis of neu—

ranging from fatigue to impaired cognitive function.

rotransmitters, such as dopamine and serotonin in the

Mineral deficiencies also lead to immune dysfunction,

brain.

impaired brain and nervous system development, the

Magnesium is the fourth most abundant mineral in

development and function of skeletal muscle, gastroin—

the body. Approximately 50% of it is found in bone and

testinal problems, and compromised bone metabolism

40% in muscles and soft tissues. Only 1% of magne-

[10]. In this section, we discuss the consequences of sium is found in blood. The physiological importance deficiencies using both animal and human models and

of magnesium lies in its role in skeletal development

consider how these might be best treated, if indeed

and in the maintenance of electrical potential in nerve

they can.

and muscle membranes. In bone, magnesium forms a

surface constituent of the hydroxyapatite mineral component. Tissue magnesium also functions as a cofactor

Extent of mineral deficiencies

for enzymes requiring adenosine triphosphate (ATP),

Deficiencies in essential minerals can occur through

enzymes involved in energy metabolism, protein syn—

several mechanisms, primary and secondary. Primary

thesis, and RNA and DNA synthesis. Calcium home—
deficiency is simply an inadequate dietary intake of
ostasis is controlled in part by a magnesium-requiring
that particular mineral. Because the fetal supply of
mechanism.
minerals from the mother is mediated through the
The selenium content of normal adult humans can
placenta, in the specific case of the fetus, a primary
vary widely, reflecting the profound influence of the
mineral deficiency can occur as a result of insufficient
environment on the selenium contents of soils, crops,
placental transfer. Secondary mineral deficiencies can
and human tissues. Approximately 30% of tissue sele—
occur through several means, including genetic dis—
nium is contained in the liver, 15% in the kidney, 30%
ease, drug interactions, and disease-associated alterin muscle, and 10% in blood plasma [7]. Selenium is ations in mineral metabolism.
an integral part of many enzymes, and during stress,
infection, or tissue injury, a number of these enzymes

Primary deficiencies – some examples

may act to protect against oxidative damage and are

The main cause of mineral deficiencies is a poor—

essential for the metabolism of thyroid hormones [8].

quality diet, often due to an inadequate intake of

Zinc is a component of more than 300 enzymes,

animal source foods, especially in vegetarians, low

where it has structural, regulatory, or catalytic roles.

socioeconomic groups, and developing countries. It

Zinc-containing enzymes are involved in the synthe—

is unlikely that a mineral deficiency would occur in

sis and degradation of carbohydrates, lipids, proteins,

isolation. The average daily intakes for women are

and nucleic acids, as well as in the metabolism of other

presented in Table 3.1. Even in the United Kingdom micronutrients. In addition, zinc acts to stabilize the and the United States, daily intake of half of these

molecular structures of a variety of DNA-binding pro—

minerals is significantly lower than the recommended

 Table 3.1 Effects of maternal mineral deficiencies during pregnancy
Maternal Fetal

Neonatal

Calcium

Preeclampsia

Premature delivery

Hypertension

Abnormal fetal development

Increased risk of adult disease

Copper

Miscarriage

Anencephaly

Low neonatal stores

Abnormal fetal development

Iodine

Miscarriage

Premature delivery

Mental retardation

Anencephaly

Abnormal fetal development

Iron

Preeclampsia

Premature delivery

Low neonatal stores

Hemorrhage

Spina bifida

Anemia

Postnatal

Low birth weight

Delayed neurological development

depression

Increased risk of adult disease

Magnesium

Preeclampsia

Premature delivery

Increased risk of adult disease

Spina bifida

Low birth weight

Selenium

Preeclampsia

Premature delivery

Miscarriage

Spina bifida

Zinc

Preeclampsia

Premature delivery

Low neonatal stores

Anencephaly

Spina bifida

Low birth weight

levels. National differences are also apparent, which is

Table 3.2 Average daily intakes

important when setting reference values and develop-

Mineral

United Kingdom

United States

ing strategies to tackle deficiencies.

Dietary-induced mineral deficiencies are caused by

Calcium

107

74

a combination of total intake and bioavailability of the

Copper

86

127

mineral in the diet. Iodine and selenium are generally

Iodine

108

efficiently absorbed by humans with more than 80%

Iron

74

69

to 100% of that available in the diet being absorbed.

Magnesium

81

78

However, the content differs with geochemical, soil,

Selenium

71

185

and cultural conditions [11]. The bioavailability of calcium from dietary components is generally less Zinc

100

120

important than the overall calcium content of the diet.

This table shows average daily intake for women between

the ages of 19 and 50 years of age in the United Kingdom

However, the calcium component of the diet has a sig-

[59, 60] and the United States [61, 62]. Intake is expressed as nificant inhibitory effect on the absorption of other a percentage of their national reference intakes.

minerals [11].

There are two kinds of dietary iron: hem-and nonhem iron. Hem iron is found in meat, poultry, and fish,

that affects the placental transfer of a micronutrient

whereas nonhem iron is obtained from cereal, pulses,

because of a defect in a copper-transporting ATPase

legumes, fruits, and vegetables. The average absorption

gene [13]. Babies born with this disorder have numer-of hem iron is approximately 25% [12]. The absorption ous problems. They are dystonic and ataxic and have of nonhem iron, copper, magnesium, and zinc is influ—

a distinctive “kinky hair” phenotype. They will nor—

enced by several factors in the diet, including the con—

mally die within the first few years of life, usually from

centration of other minerals, phytates, and protein.

aortic aneurysms. Maternal mineral intake can also be

affected by genetic diseases. For example, acrodermati-

Secondary deficiencies – some examples

tis enteropathica is an inherited disease that causes

Genetic disorders of dietary deficiencies are relatively

insufficient zinc absorption, and mothers with this dis—

uncommon, probably because most are prenatally

ease deliver babies with congenital abnormalities (see

26

lethal. Menkes syndrome is an X-linked genetic disease

Table 3.2) [14].

Chapter 3: Mineral requirements of the mother and conceptus Table 3.3 Recommended dietary allowance

cies in copper, selenium, and zinc may be rare; however, mild deficiencies are likely due to the estimated

Females aged

levels of low intake. With the increased demands of

19–50 years

Pregnancy Lactation

pregnancy added to this, it is likely that many pregnant

∗Calcium (mg/d)

1000

1000

1000

women, even in industrialized countries, will have sub—

Copper (g/d)

900

1000

1300

optimal micronutrient status.

Iodine (g/d)

150

220

290

Iron (mg/d)

18

27

9

Magnesium (mg/d)

320

360

320

Effects of deficiencies

Selenium (g/d)

55

60

70

Mineral deficiencies have varied effects because of

Zinc (mg/d)

8

11

12

the wide range of roles they play. In pregnancy, the

The values are stated as recommended dietary allowance,

effects can be seen in both the mother and her fetus

∗ except for calcium, which is stated as “adequate intake” for

(Table 3.1). The mother can suffer from pregnancy-women between the ages of 19 and 50 years [11].

induced hypertension, anemia, preeclampsia, labor

complications, and death [20].

Fetal growth and development follow a specific

Therapeutic drugs can also affect maternal mineral

timeline, and therefore the susceptibility to min—

status through altered uptake or metabolism. Several

eral deficiency will be altered throughout pregnancy.

drugs chelate micronutrients, thereby reducing cir—

Severe micronutrient deficiencies during pregnancy

culating concentrations, including D-penicillamine.

can lead to high rates of spontaneous abortion, to con—

Infants born to women who have received D—

genital abnormalities, and to stillbirth. More moderate

penicillamine during pregnancy exhibit symptoms

reductions in mineral supply can lead to placental dys-

consistent with copper deficiency, similar to those

function, premature birth, and low birth weight. Early described earlier for babies with Menkes syndrome

postnatal development is also affected with impaired

[15]. Even everyday drugs such as diuretics and neurological and immunological function. There is laxatives can have an effect on mineral status.

now growing evidence that nutrient deficiency, includ-Several disease states, including chronic diarrhea, ing minerals, during fetal development, can put the

diabetes, alcoholism, and hypertension, also alter min-child at greater risk of adult-onset diseases such as car-eral metabolism [16]. The teratogenesis associated diovascular disease, obesity, and Type II diabetes [21].

with maternal diabetes and alcoholism is associated,

in part, with the adverse affects of mineral deficiency [17]. Diseases such as malaria, as well as infection with intestinal parasites, also impair and alter the **Maternal well-being**

metabolism of multiple micronutrients [16].

Iron deficiency during pregnancy increases maternal

mortality. In fact, up to 40% of maternal perinatal

deaths may be linked to iron-deficiency anemia [22].

Extent of mineral deficiencies

It is associated with an increased risk from mater—

Iron and iodine are the two most common nutri—

nal hemorrhage, and peripartum blood loss has more

tional disorders in the world. Nearly half of the preg-severe consequences for an

iron-deficient mother. In nant women in the world are thought to be iron

addition to maternal iron deficiency, clinical investi-deficient: Even in industrialized countries, most preggations have linked low maternal serum levels of cal—

nant women suffer from some degree of iron defi—

cium, magnesium, and selenium to preeclampsia (e.g.

ciency. For example, 75% of pregnant women in Paris

[23]). One possible hypothesis for these findings is that show evidence of depleted iron stores, and only 5%

deficiencies in such minerals may inhibit the placenta's of women of childbearing age have adequate iron

antioxidant defenses.

intakes [18].

Maternal blood selenium levels are low in women

Magnesium deficiency is also thought to be com—

who experience a first-trimester miscarriage, common; approximately 20% of the population consumes

pared with women at the same stage of pregnancy who

less than two thirds of the recommended dietary

carry to term [24]. Similar evidence implicates low lev-27

allowance [19] (Table 3.3). Clinical levels of deficien-els of copper and iodine in miscarriage [25].

Section 1: Nutritional regulation and requirements for pregnancy and fetal growth Mothers who were iron deficient during pregnancy SLC46A1, which acts as both a folate and hem trans—

are likely to remain deficient into the postnatal period, porter [35].

which increases the risk of postnatal depression [26].

Investigations into two severe genetic disorders in

humans, Menkes and occipital horn syndromes, have

Fetal outcome

provided clear evidence for the essential role of cop-In the United States, approximately 3% of children are per in fetal development. These two X-linked diseases born with serious malformations, and an additional

are caused by mutations in the copper-transporting

1% die within a year from birth defects, premature

ATPase gene, ATP7A. Infants with Menkes syndrome

birth, or low birth weight [27]. Evidence continues to are characterized by progressive degeneration of the mount for the role of suboptimal maternal nutrition,

brain and spinal cord, hypothermia, connective tissue before and during pregnancy, in these effects. Much of abnormalities, and failure to thrive. These abnormali-our knowledge about the role of minerals in fetal devel-ties can all be linked to decreased activity of a number opment has been acquired from animal studies [2], and of copper-dependent enzymes [13].

these studies continue to be essential for establishing the mechanisms behind these effects [28].

Neonatal nutrition

Premature delivery is the major cause of perinatal

Exclusive breastfeeding is now recommended by all

morbidity and mortality in the developed world. There international agencies for the first 6 months of life is extensive evidence linking low maternal iron lev—

because of the benefits for infant health. The impor—

els with an increased risk of premature birth [29], and tance of the mother's nutritional status has been high-deficiencies in calcium, iodine, magnesium, selenium, lighted [36] but it is not routinely monitored. This is and zinc have now all been associated with preterm particularly important in the case of minerals such as delivery [30].

iodine and selenium, for which the concentration in

Neural tube defects (NTDs) are one of the most

milk has been shown to be sensitive to changes in the common birth defects, occurring in approximately one

maternal diet during lactation [37]. In contrast, mater-in 1000 live births in the United States. Spina bifida and nal diet has no effect on the milk content of copper, anencephaly are examples of these defects, with the

iron, magnesium, or zinc [38]. It has been shown that most severe, anencephaly, being incompatible with life.

the transport of copper, iron, and zinc into breast milk It has been estimated that up to 70% of NTDs can be

is tightly controlled by transporters in the mammary

prevented by supplementation with the vitamin folate

gland [39]. Interestingly, although the calcium content [31]. It is likely that mineral deficiencies play a role in of breast milk is not dependent on maternal intake the remaining 30% of NTDs. Evidence has now linked

during lactation, it does seem to relate to maternal cal-low maternal intakes and serum levels of iron, mag—

cium intake during the last third of pregnancy [40].

nesium, selenium, and zinc with an increased risk of

The mineral supply present in milk is believed to

spina bifida [31]; in the cases of iron and magnesium be in highly bioavailable forms [39]. For example, it this increased risk can be as great as fivefold [32]. It is estimated that infants can use more than 50% of has also been noted that offspring born to women who

the iron in breast milk compared with less than 12%

suffered from acrodermatitis enteropathica, a genetic of the iron in infant formula. The concentrations of

zinc deficiency disease, had a high incidence of malfor-minerals in breast milk decrease during the first 6

mations – in particular, anencephaly. Epidemiological months, resulting eventually in an insufficient supply evidence to support the role of zinc deficiency in anen-of minerals from breast milk later in infancy [41]. This cephaly came from studies in the Middle East, which decreasing level of nutrient supply brings into focus related a high incidence of the fetal abnormality with the importance of mineral stores accumulated by the

maternal zinc deficiency [33]. The interactions of these infant during pregnancy.

minerals with folate may also have a significant impact The infant’s gestational age and birth weight

on the incidence of NTDs and pregnancy outcome. In

strongly affect the size of stores at birth, with the fact, it has long been noted that pregnancy outcome

last fifth of gestation being critical [42]. Thereis significantly improved when folate and iron sup-fore, preterm infants may not have accumulated the plementation is provided together [34]. A molecu-required amount of mineral stores to sustain growth lar connection has been established between these

through the period in which they are exclusively

two critical micronutrients, with a protein identified, breastfed [43]. This is also likely to be the case for **Chapter 3: Mineral requirements of the mother and conceptus** full-term infants born to mineral-deficient mothers.

Models of maternal mineral deficiency are among

Several studies have shown that a normal birth weight those models clearly mimicking the human situation.

infant born to an anemic mother is more likely to

Offspring subjected to iron deficiency during gesta—

develop anemia during the first 6 months of life than tion develop hypertension, dyslipidemia, and obesity

a normal birth weight infant born to a mother with

[49]. As yet no other model of maternal mineral defi-adequate iron status [44]. There is also recent infor-ciency has shown all of these particular symptoms, but mation that extending the breastfeeding period from

maternal calcium deficiency has induced hypertension

4 to 6 months, even in infants of normal iron status, in the offspring [50], and perinatal magnesium restric-may result in iron deficiency, because the mother can-tion predisposes the offspring to insulin resistance and not give sufficient iron from her breast milk [45].

glucose intolerance [51].

Offspring development

Adaptations during pregnancy

The effects of maternal mineral deficiency persist well **and lactation**

beyond gestation and parturition. For humans, the

current evidence indicates that the brain is the organ To meet the increased demand for the essential min—

most sensitive to these prolonged effects. One of the erals during pregnancy and lactation, maternal physi—

most devastating consequences of maternal iodine

ology undergoes several alterations. Maternal intesti-deficiency is irreversible mental retardation in the off-nal uptake is increased, excretion is decreased, and spring. These effects occur because iodine is required minerals are mobilized and reutilized from vari—

for the synthesis of thyroid hormones, which in turn

ous body stores. In recognition of the increased

regulate the metabolic pattern of most organs, espe—

requirements, many government-recommended daily

cially the brain. Even mild or subclinical maternal

allowances (RDAs) are higher for pregnant and lactat—

hypothyroidism during pregnancy may have subtle

ing women than for the general population.

effects on neuropsychological development of the offspring [46]. The window of sensitivity also extends into Absorption the neonatal period because iodine deficiency in lac—

Most minerals of those discussed here are absorbed

tating women may result in insufficient iodine to the from the small intestine through both an active, sat—

infant.

urable mechanism and simple diffusion [11].

Infants who were subject to iron deficiency in the

As the demand for iron increases in the second

womb also display symptoms of impaired brain devel—

trimester, absorption increases by about 50%, and in

opment. Unfortunately, the effects are long-lasting and the last trimester it may increase by up to approxi—

may be irreversible. Children who had a low iron sta—

mately 4 times (7). Pregnancy has also been shown to

tus at birth have significantly worse language ability, increase the efficiency of absorption of calcium, cop-fine-motor skills, and emotional control (47).

per, and zinc, although to a lesser extent than demon-In the past 2 decades, epidemiological studies have strated for iron [52, 53].

shown, even within the normal range for birth weight, that there is an inverse correlation between weight at Excretion

birth and adult risk of disease and development of specific degenerative conditions, including obesity, coro-Selenium bioavailability and absorption are high even nary heart disease, stroke, Type II diabetes, cancer, and in the nonpregnant state; therefore, to conserve more depression [21]. Maternal nutrition is an important selenium, pregnancy induces a decrease in urinary factor in determining birth weight; therefore, it is now selenium excretion [52]. A similar mechanism also believed that inappropriate nutrition during gestation improves copper retention, but only by approximately

may affect the offspring's risk of developing certain 4% [53].

diseases in adulthood, a phenomenon know as fetal

programming. The mechanism(s) through which inap—

Utilization and redistribution of body stores

propriate nutrition during gestation exerts its effects To meet the increased

demands during pregnancy and

is currently unclear. To this end, several animal mod-lactation, maternal stores are mobilized, and other els have been established, using global caloric restric- maternal sources of minerals are redistributed. Some **29**

tion or alteration in a specific dietary component [48].

minerals, such as iron, have extensive stores in the

 body, as ferritin in the liver. It is estimated that a pre-by the United States and Canada (Table 3.3). The RDA pregnancy store level of 500 mg is required for the is the average daily nutrient intake level that is required mother and fetus to remain iron sufficient through—

to meet the nutrient requirements of almost all – 97% – out gestation [7]. Unfortunately, it is uncommon for of healthy individuals in a particular life stage and sex women today to have iron stores of this size, which at group. Historically, dietary reference values for preg-least partly accounts for the high incidence of iron definancy were estimated by a factorial method, combin—

ciency in pregnancy.

ing total maternal and fetal demand. The more recent

Unlike iron, there are no easily accessible stores

reference values, including those listed here, take into of calcium, magnesium, and zinc. For these miner—

account the known physiological adaptations to preg—

als, the skeleton acts as a “store,” and during pregnancy that occur in the mother. The recommenda—

nancy and lactation, these minerals are mobilized [54].

tions now also take into account the age of the mother, Bone turnover is elevated during pregnancy and lac—

because in adolescent pregnancies, intakes need to be tation. Additionally, selenium, some magnesium, and

increased by an amount proportional to the incom—

zinc can be released through tissue catabolism and

plete maternal growth at conception.

reutilized for the needs of the fetus [55].

The nutritional demands of lactation are considerably greater than those of pregnancy. Newborns dou—

Placental transfer

ble their birth weight within the first 4 to 6 months of life. For breast milk to provide all the nutritional The greatest period of fetal mineral accumulation

requirements underpinning this growth rate, it must

takes place from mid-gestation and is maximal dur—

provide an amount of energy equivalent to the total

ing the third trimester. Minerals are transported across energy cost of pregnancy. Therefore, along with the

the placenta by both passive diffusion and active

continued maternal physiological adaptation, a further transport. Selenium is passively transported across the increase in daily dietary intake is recommended for

placenta [56], and hence the fetus is critically depen-most of the minerals.

dent on maternal levels. The active transport mechanisms, especially those operating for iron, ensure that the fetus has an adequate supply of nutrients – if nec-Conclusions essary, at the expense of the maternal stores or even In conclusion, we have discussed the variety and com—

functional pools [57]. The fact that during the third plexity of mineral requirements during pregnancy. We trimester, fetal concentrations of calcium are greater have not included many aspects. For example, we have

than those in the mother indicates active transport of not discussed interactions between the micronutri—

calcium [58]. Evidence has been put forward for both ents. In itself, this is a complex and multifaceted area, passive and active placental transfer of copper, possibly and there are many interactions we do not under—

related to the stage of gestation [5].

stand. We know that iron and copper metabolism

are tightly interlinked and are beginning to compre—

Recommended daily intake

hend the mechanisms. Zinc, iron, and copper are also

An increased RDA is recommended during pregnancy

linked, but we know little about how the interactions for all but one of the minerals discussed in this chap-are mediated. Calcium and iron, iodine and selenium, ter (Table 3.3). Information on what is thought to also show mutual regulation. We have not examined be the required dietary requirement for each indi—

many studies that have tested supplementation strate—

vidual mineral is provided by many agencies acting

gies, because the literature is vast, complex, and incon-for national governments, the European Commis—

clusive. Neither have we considered the consequences

sion, and the World Health Organization. Because

of dietary overload of minerals, mainly because this is there is considerable

variation in nutrient require—

a rare problem in pregnancy. For these, more detailed ments throughout a person’s lifetime, values are given discussions, the reader is referred to the many excellent for specific life stages, including pregnancy and lac-reviews published in the British Journal of Nutrition, tation. The values are regularly updated, taking into among others. We hope, however, we have provided

account new scientific knowledge regarding the links

an overview of the fascinating and clinically essential among nutrition, health, and disease. Currently the

roles that minerals play during development, gesta-

most up-to-date dietary reference values are provided tion, and lactation.

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Section 1

Nutritional regulation and requirements for pregnancy and

Chapter

fetal growth

4Individualizedgrowthcurvesand

size at birth

Eve Blair

Measuring appropriateness

introduction of ultrasound fetometry provided a fur-

of fetal growth

ther valuable source of evidence. Estimating GA from

fetal size assumes a uniform rate and pattern of growth Growth is the rate of increase in a dimension per unit between fetuses. This assumption holds precisely in

time. Mass is the dimension traditionally considered

the hours after conception but becomes less tenable

for fetal growth because it is the most easily and accu-as pregnancy progresses. The time at which the most rately measured dimension at birth, but with prenatal

accurate estimates of GA can be made by fetometry is

imaging, prenatal growth of body parts can be monia compromise between being before discernible varia—

tored. Recognition of the importance of fetal growth

tion in growth rate develops between fetuses but after a is implicit in the importance traditionally accorded

well-defined dimension is sufficiently large compared birth weight as an indicator of pregnancy success. With with the errors in making the measurement. Measure—

increasing survival of preterm births and increasing

ment of maximum embryonal length at approximately

sources of evidence from which to estimate gestational 10 weeks gestation, before the spine has started to flex, duration, Lubchenco *et al.* [1] estimated appropriate-has been suggested as the best compromise [2]. At ness of intrauterine growth from the position on a this time, gestation can be estimated to within 5 days.

chart of birth weight by duration of gestational age

However, many women have not presented for antena-

(GA). This introduced the concept of time to the contal care by 10 weeks post-LNMP. After 12 weeks ges—

sideration of size at birth and initiated the study of tation, the smaller biparietal diameter of the head is fetal growth. An example of the now-familiar sigmoid

the dimension utilized for gestational dating by ultra-plots of observed birth weight against GA is shown sound fetometry, so the measurement error can be pro—

in Figure 4.1.

portionally greater, decreasing the precision of the GA estimate.

The importance of accurate data for

Much effort has been expended in improving the

accuracy of neonatal assessment of GA, but even the

gestational duration

most accurate measures [3, 4], which require both The belated introduction of the time dimension time and training to perform, are rather imprecise

is doubtless associated with the difficulty of accu—

with systematic biases away from term [5] and may rately measuring gestational duration, given its usually require adjustment for ethnic origins [6]. However, in occult initiation. The traditional method of estimating contrast to antenatal estimates, neonatal GA is estiGA from maternal recall of the date of commencement

mated directly as a number of weeks, rather than a

of the last normal menstrual period (LNMP) relies

date (of LNMP) or a fetal dimension on a given date,

on assumptions concerning the accuracy of recall,

minimizing the risk of recording errors, so neonatal

length of menstrual cycle and the position of ovula—

estimates tend to be reliably recorded. Thus neona—

tion therein, menstrual regularity, and an absence of tal estimates provide a valuable check on antenatal

hormonal perturbations (e.g. prior conceptions, hor—

estimates, recording errors in the data that have been mone therapies). The

evidence required to support

demonstrated to be responsible for a substantial pro—

these assumptions is frequently lacking. The reliabil-portion of the recorded GAs that were incompatible ity of the LNMP method can be enhanced by early

with recorded birth weight [7] in pregnancies resulting pregnancy testing and clinical examination, but the from extrauterine fertilization for which gestational

 Figure 4.1 Mean of male and female

5000

optimal birth weight by gestational age at

delivery and parity, estimated for births to

women of height 162 cm. (Redrawn from

Blair *et al.* [16].)

4000

3000

rams

eight g

th w

Bir 2000

1000

0

22

24

26

28

30

32

34

35

38

40

42

Gestational age (weeks)

First birth

Second birth

Third birth

Fourth birth or later

duration is accurately known. Neonatal estimates

rates of fetal growth. Comparison with these charts

therefore serve primarily to indicate gross errors in therefore overestimated the appropriateness of growth recorded antenatal estimates [8].

of neonates born at lower altitudes. Altitude is only one However achieved, an accurate estimate of GA is

of the factors responsible for differences in interfetal the first requirement for

estimating the appropriate—

growth rates; for example, the same GA girls tend to

ness of fetal growth. With GA available, growth can be weigh less than boys, taller parents tend to have larger assessed by comparing the measured gestation-specific babies, and primiparous women and women carry—

anthropometric dimension with a standard. There—

ing multiple pregnancies tend to have smaller babies.

fore, the second requirement is an appropriate stan—

When such determinants are taken into account the

dard, and the third is selection of how the comparison standard is said to be individualized.

should be made.

Obstetricians may be interested in predicting

actual birth weight if they want to make timely decisions concerning the method of delivery. In this case, Selecting a standard of fetal growth

it is appropriate to consider all known determinants of Lubchenco’s charts were derived from a population

fetal growth along with gestational duration to achieve residing in Denver, Colorado, altitude 1610 m (5280

the most accurate prediction. Factors known to be

feet), where lower atmospheric oxygen tension slows

associated with fetal growth include infant gender and **Section 1: Nutritional regulation and requirements for pregnancy and fetal growth** other genetically endowed traits, ethnicity, maternal aside, lean body weight may also

be considered a sur—

size, maternal weight gain, paternal size, maternal par-rogate for the genetic potential for body size, but the ity, plurality of the pregnancy, maternal lifestyle fac-more usually available measure of body weight during tors including nutritional status, exposure to tobacco the pregnancy is also influenced by the highly variable smoke and other toxins, altitude of residence, maternal fat mass, and for the mother, by the increasing weight medical factors including diabetes, hypertensive dis—

of the products of conception.

ease (with or without proteinuria), and infections, par-If appropriateness of growth is to be estimated from ticularly TORCH (toxoplasma, other viruses, rubella,

fetal dimensions, then duration of growth (GA) must

cytomegalovirus, herpesvirus) infections and those of be considered. In the absence of mistaken induction

the genitourinary tract. Individualized predicted fetal (or pregnancy termination), very low GA at deliv—

growth curves can be derived by statistical modeling

ery has a pathological cause; however, time itself can-that accounts for as many factors for which good data not be considered a pathological factor. Thus, GA at

are available in representative samples [9].

delivery is not a pathological determinant of weight, Because it is appropriate for different fetuses to

although certain values of GA are associated with

grow at different rates, the estimation of fetal growth growth-restricting pathologies.

may be considered in terms of appropriateness of

Maternal weight gain during pregnancy is associ—

growth given the circumstances of that particular

ated with birth weight primarily because it includes

fetus. Inappropriate growth may reflect an underly—

the mass of the fetus. It is therefore a measure of fetal ing pathology, which, if recognized, can be treated,

growth (imperfect on account of including weights

ameliorated, indicate the need for further observa—

of maternal fluid volume expansion and products

tions, or predict outcome. Furthermore, appropriate—

of conception other than the fetus) rather than a

ness of growth is frequently considered as a factor in determinant.

epidemiological research. To identify appropriateness The maternal contribution to fetal growth includes

of growth, an obvious standard for comparison is the

both her genetic contribution to the fetus' growth

optimal growth trajectory, how the fetus would grow

potential and her ability to provide fetal nutrition.

in the absence of any pathological factors affecting its The latter will be limited by the uterine area avail—

growth. In such circumstances, the only factors deterable for placentation, for which maternal height may mining the rate of growth would be nonpathological.

also be considered a surrogate. Thus, maternal size is a stronger determinant of

fetal growth than is paternal Nonpathological determinants

size, particularly because, at least in population studies, the identity of the father is seldom confirmed.

of fetal growth

Birth weight has frequently been observed to vary

Fetal sex is perhaps the only incontrovertibly non—

with ethnicity [10]. However, mean maternal size, ges-pathological factor, but many others are usually non-tational duration, and social, economic, and nutri—

pathological or unalterable, particularly once fetal

tional status can vary significantly between ethnic

growth is being assessed.

groups, as can the frequency of growth-determining

Chromosomal anomalies, genetic anomalies, and

pathology. All these factors should be considered when factors resulting in other birth defects may affect fetal comparing optimal growth trajectories between ethnic

growth, and it is safest to exclude all births with

groups, particularly those with the strongest effects on birth defects from the population from which opti—

birth weight – namely, gestational duration, maternal mal growth trajectories are derived. Parental growth

size, and frequency of growth-restricting pathologies.

potential dictates the growth potential of their off—

When these are adjusted for, differences in growth tra-spring. This is usually

reflected in parental stature, jectory tend to diminish. For example, the consistently unless the parents' genetic potential for growth has

lower weights of births to Aboriginal women in West—

not been realized, as may occur, for example, follow—

ern Australia have been shown to be almost entirely

ing exposure to nutritional deprivation in childhood.

explained by a slightly shorter mean GA, a higher bur-In developed countries, childhood nutritional depri—

den of recognized growth-restricting pathology, and

vation is unusual, and parental heights may be consid-tobacco smoke exposure. With the unquantifiable con—

ered a surrogate measure of the inherited potential for tribution attributable to social disadvantage, it was **36**

growth to adulthood in their offspring. Bodybuilders

concluded that these factors were responsible for the **Chapter 4: Individualized growth curves and size at birth 100**

Figure 4.2 Distribution of gestational

duration at delivery for singleton neonatal

survivors: Western Australia, 1980–2000.

10

%

1

23

24

25

26

27

28

29

30

31

32

33

34

35

36

37

38

39

40

41 >=42

0.1

0.01

Gestational duration, weeks

lower birth weights rather than any ethnic difference pregnancy, maternal height and parity, and, when

in optimal fetal growth rate [9]. Obviously, maternal paternity is known with certainty, paternal height.

lifestyles and medical pathologies adversely affecting Pregnancies affected by any of the pathological deterfetal growth must be considered pathological.

minants of fetal growth should be excluded from

The increasing fetal growth rate with increasing

the population from which the optimal standards are

parity (Figure 1) has been attributed to what has been derived (e.g. Blair 2005).

termed priming of the uterus or irreparable damage

to the epithelium of the spiral arteries. This facilitates Birth weight versus estimated fetal weights

nutrient transfer through uterine blood vessels in subsequent pregnancies. At which parity does optimal and statistically modelled trajectories

growth occur? The best pregnancy outcomes are asso—

Growth charts were initially constructed from the

ciated with second and third births, but selection by observed median birth weight of infants born in each

social and medical factors may be more responsible

gestational week. Problems with this method include:

for this observation than any effects attributable to 1. The decreasing number of births with decreasing

variations in fetal growth. Because first pregnancy is GA; see Figure 4.2.

unavoidable if there is to be a second or third, parity is 2. The bi-or multimodal distribution of birth weight usually considered a nonpathological determinant of

observed at low gestations.

fetal growth, although biologically fetal growth in the 3. The observed increase in dispersion of weights

first pregnancy may be considered restricted. Similarly, about the mean weight with decreasing gestation.

fetal growth is curtailed in a multiple pregnancy when 4. The pathological causes of preterm birth may

the sum of fetal demands approaches the maternal lim—

impair fetal growth, and preterm born infants

its of supply. Naturally this occurs earlier in pregnancy tend to be systematically growth restricted relative

as the number of fetuses increases. This may account

to infants of the same gestational age whose

for at least some part of the less optimal outcomes of pregnancies continue to term.

multiples born after the onset of multiplicity-related growth restriction than those of singletons born at the The nonuniform GA distribution could be addressed

same gestations. However, because pregnancy reduc—

by selecting several preterm birth cohorts to each term tion, at least of twin pregnancies, is seldom desired cohort, the sampling multiple increasing with decreas-nor are the hazards warranted, it is reasonable to coming GA. However, to achieve a sample with a simi—

pare growth with a standard optimal for a given multilar number of births before 28 weeks as at term, the plicity, thus treating multiplicity as a nonpathological

sampling multiple for births less than 28 weeks would determinant of growth.

approximate an unachievable ∼110-fold.

The optimal growth curve should therefore be indi—

The second and third observations are biologi-

vidualized to the individual’s sex, multiplicity of the cally counterintuitive and arise primarily as a result **Section 1: Nutritional regulation and requirements for pregnancy and fetal growth** of errors in the recorded GA. Some errors are sys-term, or is it possible to select normally grown preterm tematic on account of breakthrough bleeding at 4—

born infants? From the 1998–2002 cohort of West—

week intervals early in pregnancy, the frequency of

ern Australian Caucasian singleton neonatal survivors, which decreases rapidly at each 4-week interval. If this pregnancies affected by the factors most frequently

bleeding is mistaken for a normal menstrual period,

associated with pathological deviations in growth were GA estimated from LNMP dates, even if certain and

excluded. These factors were maternal smoking, vas—

accurately recorded, will be systematically underesticular disease or diabetes, birth defects, or TORCH

mated by 4 weeks or, less frequently, by 8 weeks [11,

infections [16]. These criteria excluded 37.6% of the 12]. Even though only a small proportion of births population that were born at term, 54.4% of those are likely to have such systematically underestimated born 33–36 weeks GA, and 76.6% of those born Ↄ33

gestations, because the vast majority of births occur weeks GA, confirming that the frequency of growth—

at term or near term (Figure 4.2), the small propor-deviating pathology is associated with gestation of tion of term and near-term births with systematically delivery. However, we had no reason to believe that

underestimated GAs contributes a significant propor—

the remaining 23.4% of those born Ↄ33 weeks (n =

tion of those recorded as being born 4 or 8 weeks ear-334), 45.6% of those born 33–36 weeks (n = 2522), lier, creating multimodal distributions. The extremely and 62.4% of term births (n = 59 557) would be abnor—

nonuniform GA distribution also means that random

mally grown and used the characteristics of these

errors increase the distribution of birth weights at less births to derive equations for optimal growth curves

frequently occurring GAs to a greater degree than

that included terms for fetal sex, maternal height, and the more frequently occurring. GA errors, particularly parity.

the systematic 4-and 8-week gestational overestima—

The development of individualized growth curves

tions, can be largely eliminated when they most affect has been made possible by the increasing sophistica—

median birth weight by setting upper limits to accept-tion of computer software that fits statistical models able birth weights in the GA range at which growth is (equations) relating a continuous outcome (e.g. birth sufficiently rapid for there to be little overlap between weight) to many variables. These may be plotted as in weight distributions 4 gestational weeks apart [13, 14].

Figure 4.1 for specific sets of circumstances, but an The fourth problem, the tendency of preterm equation is both more flexible and robust because it

births to be growth restricted, initially recognized

represents all possible circumstances. Therefore, indi-by Lubchenco *et al.* [1], is the most intransigent. In vidualized growth curves are usually presented by

response, intrauterine growth charts have been con—

equations for median weight rather than graphs.

structed from fetal weights estimated from fetometric measurements taken throughout gestation on infants

How to “measure” appropriateness

subsequently born at term. The problem with these lies in the accuracy of the estimating equations. System—

of growth

atic weight overestimation is likely because the equa-Lubchenco et al.’s growth charts [1] presented a series tions relating fetal weight to fetometric dimensions

of percentile positions on the birth weight distribution are derived from births that must necessarily occur

observed in each gestational stratum, the 10th being

after, usually up to 7 days after, the measurements

the lowest percentile presented and the 90th being

were made. It also assumes that the shape of preterm

the highest. Much clinical practice involves making

born infants will reflect those of infants at the same decisions – for example, differentiating normal from

gestation who are subsequently born at term. Dudley,

abnormal, so observations tend to be categorized. This systematically reviewing the performance of such

occurred in the study of fetal growth, and traditionally equations [15], concluded that random errors were those with weights below some cutoff point, often the large, with systematic overestimation of low-and

10th percentile position, occasionally 3rd percentile or underestimation of high-weight fetuses and ques—

two standard deviations from mean, are categorized as tioned the validity of such equations, even without tak-small for their gestational age (SGA) and those above ing into account the delay in weight measurement in

the 90th as large for gestational age (LGA), implying the data from which the equations are derived.

that these weights are less appropriate than intermedi-Do all preterm born infants grow abnormally relate weights. However, these cutoff points are arbitrary: **38**

ative to their gestational peers subsequently born at births identified by lower cutoff points are more likely **Chapter 4: Individualized growth curves and size at birth** to be pathologically growth restricted, but a greater ence, its diameters, femur length, and, most sensitively proportion of pathologically growth-restricted infants in the third trimester, abdominal circumference.

will be excluded than with higher cutoff points. It is frequently desirable to have a measure of the degree of **The role of maternal nutrition**

inappropriateness, and percentile position has significant drawbacks as a quantitative variable and is sub-in fetal growth optimal even as a categorical variable because:

The conceptus is initially nourished in a low-oxygen

r

environment by polyols secreted from the uterine

Percentiles are ordered, but not interval, measures

walls. This appears to be quite immune to external

in which the difference in the dimension between

manipulation in naturally occurring conceptuses, but

adjacent percentiles at the extremes is very much

after a placental supply has been established, maternal greater than those in the middle of the

nutritional status has a complex relationship with fetal distribution, presenting limited valid analytical

growth, much researched in the interests of animal

possibilities and a great potential for

husbandry. However, the relevance of animal research

misinterpretation.

r

to human pregnancy and diets is questionable, and

Extreme percentile positions (those frequently of

only human data are discussed here. A significant

most interest) are at the extremes of an

proportion of the human literature reports observa—

approximately Gaussian distribution where

tional data from which it is not possible to differen-observations are sparse and most subject to error.

tiate cause, effect, or merely noncausal associations They are therefore the least precise and the most

mediated by factors such as social class. Such stud—

sensitive to data quality.

r

ies serve primarily to suggest nutritional hypotheses Extreme percentiles are the most sensitive to the

that should be tested in randomized controlled trials incidence of growth-disturbing pathologies in the

before dietary interventions can be recommended. The

population and vary most with the health of the

evidence reported here is therefore confined to ran—

population used as the standard [16].

domized controlled trials or other experimental settings where the nutritional interventions were not self-Percentile positions should therefore be abandoned in selected.

favor of a more generalizable, continuous measure of

There are methodological challenges in the study

which the ratio of observed dimension to an individu—

of nutritional supplementation in human populations

alized value of the dimension at peak observation den-associated primarily with the initial nutritional status sity is an obvious example. For birth weight, this ratio of subjects. Neglect of these challenges may account for has been termed the birth weight ratio [17], the indi-the confusion in the literature, spawning many system-vidualized birth weight ratio [18], or, more descrip-atic reviews and even a review of systematic reviews tively, the proportion of optimal birth

weight [16].

[19]. A nutritional supplement is of benefit only if the Birth weight is often considered because, for many supplement is a biological requirement and not already pregnancies, the sole assessment of growth is made at present in sufficient quantities. Additional supplemen-birth. However, a better appreciation of growth can be tation may even be detrimental. Therefore, if the ini-obtained by comparing the growth trajectory of spe—

tial status of research subjects is heterogeneous with cific fetal dimensions throughout gestation with an

respect to the nutrient, the results of its supplementa-individualized standard. This allows the differentiation tion can also vary. Nonetheless, a few comments can

of fetuses for whom the dimension follows a similar

be made.

trajectory to that of fetuses without growth-restricting Under famine or near-famine conditions, fetal

pathology (for whom the proportion of optimal ratio

growth appears increasingly restrained by a lack

will remain constant) from fetuses with a faltering

of maternal energy supply as pregnancy progresses.

of the initial trajectory, for whom the proportion of Observations made following the unique event of

optimal will drop. After the possibility of measure—

the short-term Dutch famine during World War II

ment error has been eliminated (by replicating obser—

indicate that birth weight was most affected when

vations), the later are growth restricted, whatever their famine was experienced only in the second half of

birth weight. The dimensions most often measured

pregnancy [20]. In developing countries, maternal **39**

fetometrically for this purpose are the head circumfer-macronutritional deficiencies can occur frequently **Section 1: Nutritional regulation and requirements for pregnancy and fetal growth** and have been successfully addressed by balanced mentation with 1000 mg vitamin C plus 400 IU vita—

protein/energy supplementation [19, 21]. The effects min E was associated with a small, statistically insignif-on birth weight tend to be small, and the benefits icant increase in the frequency of preeclampsia. These may be better measured by perinatal mortality [22,

differences could have been due to chance because all 23]. High protein supplementation (C20% of energy trials had similar levels of vitamin supplementation provided as protein) has repeatedly been shown to

and much higher than recommended daily intakes,

reduce fetal growth in both the developed and devel—

and most subjects lived in developed countries. How—

oping world, although protein-induced birth weight

ever, they varied with respect to subject selection crite-reduction may not be accompanied by the antici—

ria. The latest, largest trial selected primiparae between pated increase in perinatal mortality [22]. Maternal 14 and 22 weeks in whom more than 90% of both inter-macronutritional deprivation is rare in the developed vention and control groups had adequate vitamin C

world, and efforts to increase the reduced birth weight intake, and approximately 43% had adequate vitamin

seen in underprivileged women in the developed

E intake before supplementation. The trials included

world by macronutrient supplementation tend to be

in the earlier systematic reviews selected women at

unsuccessful.

higher a priori risk of preeclampsia, and their vitamin In the developed world, the major causes of fetal

status before supplementation was not known.

growth pathology are maternal vascular disease, par—

Whether the initial vitamin status of subjects can

ticularly preeclampsia, maternal infections, particu—

explain the observed differences for vitamin C and E

larly of the genitourinary tract, chromosomal and

supplementation, the systematic review of the calcium genetic anomalies, and, increasingly, syndrome X, the supplementation to prevent preeclampsia [27] makes metabolic anomaly that includes diabetes and insulin it clear that calcium supplementation is beneficial only resistance. There is some evidence that these may

to women with low initial calcium intake.

respond to micronutritional therapy. However, as with If nutritional supplements can be beneficial only if

macronutrient therapy, micronutrient therapy is ben—

they are lacking, the question is whether any essential eficial only if the specific nutrients being supplied are vitamins and minerals are routinely lacking in preg —

lacking initially and are supplied in a timely fashion.

nant women in developed countries. There is a significant minority of women who appear to require

Nutrient supplementation and

more folate than is obtained from their diet to avoid neural tube defects, and many women are chroni-

fetal growth

cally short of iron because of menstruation. Thus, their The literature related to preeclampsia is given as an routine supplementation appears defensible. Random —

example. Preeclampsia affects up to 5% of all pregnanized controlled trials have shown that iron supple—

cies, depending on its definition. It is associated with mentation can increase birth weight in Zimbabwe

raised maternal blood pressure, proteinuria, and fetal [30], and a systematic review concluded that the growth restriction; if severe, it can be life-threatening decrease in proportion of low birth weight and SGA

to both mother and child. It is more likely to occur

babies following multivitamin supplementation was

in primiparae and in women with a family history of

attributable entirely to the iron and folate compo—

preeclampsia or a history of preeclampsia in previous nents [31], although a randomized controlled trial pregnancies. It has been variously suggested that vita-from Nepal observed a mean gain in birth weight of min D [24], marine oils [25], vitamins C plus E [26],

77 g when 13 micronutrients were added to iron and

and calcium [27] can each protect against preeclamp-folate supplementation, somewhat more than might sia, but the results of randomized controlled supple —

have been anticipated from the 1.2-day increase in

mentation trials have been confusing. Two Cochrane

gestational duration. However, such trials tend to be systematic reviews published in 2005 suggested that

conducted in developing countries, and Milman [32]

vitamin C (five trials and 766 women)[28] and vitamin sounded a word of caution, pointing out that iron neg-E (four trials, 566 women)[29] may alone or in com-atively influences the absorption of other divalent met-bination reduce the incidence of preeclampsia with als (which includes calcium) and should not be supple-relative risks approaching statistical significance. The mented if ferritin is present at more than 70 g/l.

authors concluded that insufficient data were available It has been argued that because the diet afforded by

40

and conducted a much larger trial in which supple—

modern mass market agricultural methods is depleted

Chapter 4: Individualized growth curves and size at birth in many vitamins and minerals relative to diets proto add adequate balanced macronutrition throughout

duced at a more leisurely pace [33], and because health pregnancy, but this is an unusual problem in developed promotion messages to minimize exposure to sunlight

countries where an oversupply of macronutrients lead—

in the interests of avoiding skin cancers have resulted ing to obesity and diabetes

poses greater problems.

in a population tendency to vitamin D deficiency [24],

it may be advisable even for women with apparently

Summary Table

adequate diets to take a balanced multivitamin sup—

Obtaining an individualized growth curve

plement before and during pregnancy. However, the

r Decide whether you want to (a) identify optimal

possibility of detrimental effects with oversupplemen-size or (b) predict actual size.

tation (as with iron or protein) and the likelihood

r

of inappropriate supplementation, demonstrated to be

Choose the fetal or newborn dimension of

common in Finland [34], suggest that the conclu-interest.

r

sion arrived at by Ramachandran [35] in India, who Choose the variables on which you wish to stated that each women should be assessed individu—

individualize: (a) nonpathological determinants of

ally before appropriate dietetic advice can be given, is fetal growth, (b) all known and measurable

universally applicable.

determinants of fetal growth.

r

Fetal growth has a tightly programmed sched—

Choose from the literature or derive a standard

ule. After a stage has passed, it cannot be revisited.

that addresses the variables on which you wish to

Therefore, when deviation from an established fetal

individualize or is derived from a population with

growth trajectory is recognized, it is too late to correct characteristics similar to the index individual.

that deviation by addressing any nutritional imbalance Estimating appropriateness of growth

that may have caused it. Any recognized nutritional

r Estimate GA of the index individual as accurately

deficiency should of course be rectified because this as possible.

may prevent further disadvantage and will assist the

r Obtain the optimal dimension estimated for the

woman in recovering from the pregnancy, but for opti—

individual by solving the chosen standard

mum fetal growth, women must enter pregnancy in a

equation for the values of the determinants

nutritionally optimal state. The use of individualized appropriate to the

individual, including GA.

growth curves cannot do much to direct nutritional

r Divide the observed value of the dimension by the

advice for the index pregnancy, although it can inform optimal value, multiply by 100 to give a

such advice for subsequent pregnancies and for the

percentage; 100% indicates that the newborn is

woman’s recovery.

optimally grown, and the further from 100%, the

Conclusion

less appropriate the individual’s growth.

r For birth weight, ratio values between 85% and

Individualized fetal growth curves can be used to

115% are generally considered normal.

assess the appropriateness of fetal growth given the

r For longitudinal fetometric measurements, note

nonpathological characteristics or predict size at birth the ratio at each assessment. A constant ratio

given all growth-determining characteristics of the

indicates an appropriate growth trajectory.

pregnancy. Fetal growth may be affected by the

mother’s nutrition throughout her life. In developed

Predicting actual size

countries, adequate micronutrition before conception

r Solve the chosen standard equation for the values

and avoidance of teratogens in early pregnancy are

of the determinants appropriate to the individual,

the nutritional factors most relevant to optimal fetal where GA takes the value at which delivery is

growth. In developing countries, it may be necessary

anticipated.

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43

Section 1

Nutritional regulation and requirements for pregnancy and

Chapter

fetal growth

5 **Maternaldietsinthedevelopingworld** Shobha Rao and Chittaranjan Yajnik

underlying determinants of ill health have changed

r Poor fetal growth in the developing world is

[1], for in many Asian countries, childhood malnutri-largely attributed to widespread maternal tion continues to be a major public health problem.

undernutrition.

High prevalence of low birth weight (LBW) contin—

r In most developing countries in Asia and

ues to be a major nutritional concern. Eighty percent Africa, the rates of low birth weight are above

of all newborns with LBW at term are born in Asia;

20%, calling for Public Health action.

approximately 15% and 11% are born in middle and

r Low birth weight is prone to reduced growth,

western Africa, respectively; and 7% are born in the

altered body proportions, and a number of

Latin American and Caribbean regions [2]. The major-metabolic and cardiovascular changes.

ity of LBW in developing countries is due to intrauter-r ine growth restriction (IUGR), whereas most LBW in

In addition to a woman’s good nutrition

industrialized countries results from preterm birth.

throughout life, a sociodemographic

High prevalence of LBW in developing countries is

environment that is conducive to sustaining

therefore a reflection of a more severe problem related optimal fetal growth is necessary.

r

to maternal undernutrition.

Maternal diets in the developing world are

Poor fetal growth in the developing world is largely

inadequate in major macronutrients.

attributed to widespread maternal undernutrition. In

Moreover, cultural beliefs, practices, and

fact, poor nutritional status at conception, low gesta-food taboos greatly influence maternal tional weight gain due to inadequate dietary intake,

intake.

r

and short maternal stature due to mother’s own child—

Multiple micronutrient deficiencies exist

hood undernutrition or infection are believed to be

because of inadequate food intake, poor

the major determinants for LBW in developing coun—

dietary quality, poor bioavailability, or a

tries [3]. Infants born with LBW suffer from extremely combination of these factors.

high rates of morbidity and mortality, underweight,

r Systematic research is essential to identify

stunting, or wasting through childhood. Moreover,

micronutrients of potential interest, examine

recent studies provide evidence for the association

whether intervention at the preconceptional

of intrauterine undernutrition with increased risks of stage could have an impact on fetal growth,

adult disease. The implication is that even before elim-explore food-based interventions and test inating the long-standing problem of undernutrition,

their efficacy, and so on.

developing countries such as India face epidemics of

diabetes, hypertension, and coronary heart disease.

Maternal nutrition is thus of paramount importance

and requires critical understanding to plan effective

Introduction

strategies. In particular, identifying effective time win-

In recent years, several developing countries, espe—

dows for nutritional interventions to adolescents or

cially in Southeast Asia, have seen relative prosperity, pregnant women, understanding the role of macro—

middle-class affluence, and unprecedented economic

and micronutrients in fetal growth, and consider—

development. It is uncertain, however, whether this has ing the importance of various nonnutritional fac—

been associated with improvements in health, espe—

tors are some of the major issues that require urgent **44**

cially that of women and children, and whether the

attention.

Chapter 5: Maternal diets in the developing world 50

function, which may be sustained throughout child—

40

>15% LBW and > 20% IUGR =

hood [5–7].

Major public health problem

Among survivors of LBW, another important prob—

30

lem is childhood growth. Most LBW children remain

%

20

shorter and lighter as adults. Similarly, the impact

10

on neurological function is yet another adverse effect 0

that LBW babies face, and it is not clear whether

es

existing interventions directed toward these infants

India

anmar

Pakistan

i Lanka

Maldiv Sr

My

will improve their cognitive outcome. In developing

Bangladesh

countries where children are exposed to poor nutri—

Source: de Onis *et al.* (1998) *Eur J Cl Nutr* 52(S1):S5.

tion, high levels of infection, and other conditions of Figure 5.1 Incidence of low birth weight at term in selected Asian poverty, the long-term development is dependent on countries . (From de Onis M, Bl össner M, and Villar J, Levels and the quality of their environment. Because LBW occurs patterns of intrauterine growth retardation in developing countries.

European Journal of Clinical Nutrition [1998], 52[Suppl 1]:S5–15.) more often in deprived environments, it can serve as a marker of associated poor outcomes throughout life.

The recent hypothesis on fetal origins of adult

Prevalence of LBW in developing world diseases suggests that fetal undernutrition at critical The geographical incidences of LBW at term in

periods of development in utero and during infancy

selected Asian countries show that Bangladesh has the leads to permanent changes in body structure and

highest incidence (∼40%), followed by India and Pak—

metabolism [8–11]. Adults born with LBW suffer an istan (between 20% and 25%; Figure 5.1). In most increased risk of high blood pressure, obstructive lung developing countries in Asia and Africa, the rates are disease, high blood cholesterol, and renal damage. In above 20%, calling for public health action.

short, those of LBW are prone to reduced growth,

The majority of LBW in developing countries is due

altered body proportions, and a number of metabolic

to IUGR, the causes of which are complex and mul—

and cardiovascular changes. The hypothesis not only

tiple, depending primarily on the mother, placenta,

has brought a paradigm shift from genetic explana—

fetus, and combinations of all three. The countries

tions of noncommunicable disease to phenotypic ones

where high proportions of LBW are seen are also the

but has also emphasized the overwhelming impor—

countries where women have low body mass index

tance of maternal nutrition. It further implies that

indicating maternal undernutrition. Although poor

improving nutrition of young girls and women is prob—

maternal nutritional status is a major determinant of ably the important step toward the prevention of LBW

LBW, the factors responsible range from sociodemo—

and its accompanying disease burden to break the cycle graphic to genetic, illustrating a wide spectrum of

of intergenerational undernutrition and LBW.

underlying causes. To arrive at effective strategies to combat the problem of LBW, it may be necessary to

Maternal undernutrition before

first look into the short-and long-term implications of LBW. For example, maternal nutritional interven-

conception

tions could be short-term remedies, whereas educa—

Although large-scale food shortages and famines are

tion, gender discrimination, and poverty must be dealt now uncommon, rates of maternal malnutrition in

with through long-term strategies.

the developing countries are among the highest in

The risk of neonatal death for infants who weigh

the world. Countries with a higher percentage of

between 2000 and 2499 g at birth is estimated to be

LBW generally have a higher percentage of women

4 times higher compared with those weighing 2500

with low body mass index (BMI). Several studies

to 2999 g and 10 times higher compared with those

have reported a positive correlation between mater—

weighing 3000 to 3499 g [4]. Apart from high mor-nal anthropometry (weight/height/BMI) and birth tality risk, various studies have shown the relation of weight [12, 13]. Undernutrition evident by decreased LBW with risk of morbidity. In India and Bangladesh, maternal height (stunting) and below normal pre—

more than half of the deaths due to pneumonia could

pregnancy body weight and pregnancy weight gain are

be prevented if LBW were eliminated. In fact, LBW is

among the strongest predictors of LBW. Pre-pregnancy

also implicated as a contributor to impaired immune

body weight and gestational weight gain have an

 Figure 5.2 Relative importance of Ge

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established factors with direct causal

impact on intrauterine growth retardation

Maternal LBW a

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(IUGR) in rural developing countries. (From

Kramer,3 figure 1, P.2.)

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independent but cumulative influence on birth weight

growth and neonatal abdominal and mid upper arm

(Figure 5.2).

circumference [19].

A better understanding of the relationship of birth

Studies in Jamaica have in fact indicated that in

size to maternal nutrition is critical for planning

humans, poor dietary status before conception may be

effective interventions to improve birth weight. Howa risk factor for LBW and also for elevated blood pres-ever, the relationship is not yet clearly understood.

sure in offspring [21]. Additionally, our work on Wis-Studies that investigated the relationship are scarce, tar rats has clearly demonstrated that poor nutritional and those that are available are inconsistent [14].

status before conception may show influence on func—

This relationship is influenced by many biological and tioning of vital organs by way of inflated glucose and socioeconomic factors that vary widely among differ —

cholesterol levels in offspring at later ages [22].

ent populations. For example, it differs among ado—

The populations in which proportions of moth—

lescents [15], among women from low socioeconomic ers with low BMI are high are also the populations in class [16] who have poor nutritional status before con-which several sociodemographic factors have a signif-ception, and even in most developed countries such as icant impact. For example, in countries such as India Austria, where women have cosmetic undernutrition

where son preference is high, most girls experience

[17]. India’s poor fetal growth is at least partly caused undernutrition from childhood. It is known that a girl by maternal chronic energy deficiency and stunting

child is less likely to be breastfed and receives less [18]. A study from rural Maharashtra, India, reported medical treatment during illness because of gender that size at birth was strongly predicted by mater—

bias. In fact, it has been reported that beyond the age nal pre-pregnancy nutritional status [19]. Inadequate of 5 years, the nutritional intakes of female children maternal nutrition around the time of conception is

are lower than male children in every age group [23].

reported to be associated with nongenetic congeni—

A review of Indian studies shows that girls have greater tal abnormalities and LBW [20]. Maternal weight is mortality rates in infancy, shorter periods of breast-a composite of the mother's own intrauterine, infant, feeding, less varied diet during preschool and school childhood, and pubertal growth, as well as of energy

age, and less attention paid to their health compared and protein balance in adult life. Her nutritional expe-with boys [24]. Continuation of slow and gradual riences at these different times are reflected in her head height growth even beyond 18 years has been reported

circumference, height, fat, and muscle mass. A strik—

in undernourished children from poor communities.

ing new finding of the Pune Maternal Nutrition Study

The continuation of growth at later ages raises sig-

(PMNS) was that maternal head circumference was

nificant concerns, especially in the case of rural girls **46**

the measurement most strongly related to overall fetal who marry at an early age and have early conception.

Chapter 5: Maternal diets in the developing world Percent Women

intrauterine life tends to produce small but normally **BMI<18.5 kg/m2**

proportional animals, whereas undernutrition later in **50**

41.1

40.5

development leads to selective organ damage and disproportionate growth. A major difference in developed and developing countries is that proportional

25

22.4

growth retardation is common in developing coun-

18.7

14.6

tries, whereas disproportionate growth retardation is **7.2**

common in developed countries. Asymmetrical IUGR

infants have better prognoses for long-term growth

0

S Asia

SE Asia

China

SS Africa

C Amer.

S. Amer.

and development than do symmetrical IUGR infants.

ACC/SCN,1992

Poverty is a basic underlying cause of maternal

Figure 5.3 Chronic energy deficiency in women aged 15 to malnutrition in most poor communities of the devel—

49 years.

oping countries. Maternal diets are therefore mainly

lacking in major macronutrients. In India too, despite Adolescent pregnancy is known to increase risk for

large differences in habitual dietary patterns in differ-pregnancy wastage and LBW [15], even in Western ent States of India, several studies report low dietary populations. The case becomes worse for rural under—

intakes of energy and protein [27–29]. Many of the nourished girls, for whom nutritional stress begins earlier maternal interventions were therefore con—

in childhood and continues through adolescence into

centrated on supplying energy and proteins. How—

adulthood. Low dietary intake and participation in

ever, studies of energy protein supplementation during farming activities demanding higher energy lead to

pregnancy have produced varying and sometimes con—

sustained energy deficits. A majority of young married flicting results [30], although the most recent RCT trial girls from developing countries thus have poor nutri-from the Gambia has reported that a high energy, ante-tional status before conception and need urgent atten-natal dietary supplement can increase maternal weight tion (Figure 5.3).

gain, reduce LBW by 35%, and significantly reduce

One of the social factors that has been shown to

stillbirth and neonatal deaths by 55% and 40%, respec-have a significant impact is maternal literacy. Mater-tively [31, 32].

nal education is shown to be significantly associated Cultural beliefs, practices, and food taboos also

with age at marriage, age at first delivery, seeking ante-play a role to some extent in determining maternal natal care, and having hospitalized care, all of which intakes in some of the populations in developing coun-are known to have an effect on birth weight [25]. These tries. For example, in rural populations in India, foods observations not only highlight the importance of

such as chicken, meat, eggs, banana, or papaya are con-good nutrition throughout a woman's life time but also sidered to be "hot" foods that cause abortion and are indicate the need for a sociodemographic environment

prohibited during pregnancy. Similarly, social beliefs that is conducive to sustaining optimal fetal growth.

such as that the desire for more sleep during pregnancy is a sign of female fetus or that working until late gestation results in easy delivery in fact have adverse influ-Maternal nutrition – macronutrients ences on pregnancy outcome. Further, in the absence

Maternal malnutrition has been shown to be associ—

of medical facilities in rural areas, especially in remote ated with fetal malnutrition, and estimates of IUGR in or tribal areas, maternal intakes are intentionally kept the less developed countries, especially those in South low to prevent a baby from becoming big and thus

Asia, range from 25% to 50%. Nutritional deficien—

reducing difficulties at the time of delivery. All such cies are common in women of reproductive age in

beliefs and practices clearly contribute to the problem developing countries, with epidemiological and bio—

of LBW.

logical studies suggesting that specific nutritional defi-In many poor communities in the developing ciencies can contribute to maternal morbidity and

in

world where LBW is a major problem, women are

turn affect the pregnancy outcome. Similarly, nutri—

often involved in hard work such as farming activ—

tional insults during different periods of gestation have ities throughout gestation. The impact of maternal

differing effects on birth. Early work of McCance and activities on birth size, combined with low nutritional **47**

Widdowson [26] showed that undernutrition in early intake, cannot be overlooked. Among rural mothers **Section 1: Nutritional regulation and requirements for pregnancy and fetal growth** enrolled in the PMNS, it was observed that maternal with those who delivered normal weight babies, it

activity was inversely related to birth size even after was observed that the maternal diets in the for—

adjusting for maternal confounding variables. In par—

mer group were deficient in folate, iron, and cal—

ticular, a strenuous activity such as fetching water from cium [38]. Although nutrient requirements in the first the well was associated with lower birth weight [33].

trimester are quantitatively small, nutritional depriva-Reported studies [34] show that farming communities tion during this period can adversely affect placental often are exposed to seasonal energy stress because of structure and indirectly ultimately the birth weight.

slack and harvest periods that greatly affect the mater-Deficiencies of vitamin A, folate, and iron may be asso-nal intakes. In fact, it has been shown that prevalence ciated with growth retardation, whereas supplementa—

of LBW differed significantly in these seasons. Further, tion with calcium and

manganese may increase birth

it was observed that reduction in activity can influ—

weight and length [39]. Placental and fetal growth is ence birth size, especially during harvest season, when thus most vulnerable to maternal nutrition (protein

more food is available. The implication is that materand micronutrients) status in the early pregnancy (first nal activity can be a modifiable factor to improve birth trimester), a period of peri-implantation and of rapid size in farming communities.

placental development [40]. This has been also supported by an observational study showing that onset of coronary artery disease was earlier among persons

Maternal nutrition – micronutrients conceived during the Dutch Famine [41].

In most populations, maternal diets are inadequate in Although maternal undernutrition in developing

both macronutrients and micronutrients. However, it

countries is often in the form of multiple micronu—

cannot be denied that macronutrient deficiency has

trient deficiencies, the literature linking maternal

received by far the most attention, and as a result

micronutrient status with birth size is dominated

energy/protein-rich interventions are under way in

by studies of single micronutrients [42]. One of the many developing countries. Among reasonably well-major findings of the PMNS was that consumption nourished women of industrialized countries, mater—

of micronutrient-rich foods such as green leafy veg—

nal diet has at most a small impact on placental and

etables, fruit, and milk was significantly associated birth weights, but it may be an important determinant with fetal growth (Table 5.1) [43], even after adjust-of fetal growth in developing countries [35]. Maternal ing for maternal confounding factors. Furthermore, micronutrient deficiencies are less recognized. How—

this association was even stronger among undernour—

ever, available data on the relationship between mater-ished women (Ↄ40 kg, *i.e.* below the lowest tertile of nal micronutrient status with actual pregnancy out—

maternal pre-pregnancy weight). In this population,

come is scarce. In India, more than 60% of women

birth size was not associated with energy or protein

suffer from folate deficiency, and those deficiencies intake but was associated with consumption of these

are greater in magnitude during pregnancy. Subclin—

micronutrient-rich foods. These observations suggest

ical vitamin deficiencies suffer from subtle functional that micronutrients play an important role when

deficits. It has been shown using animal models that

macronutrients in the maternal diet are inadequate.

pups born to dams fed a 50% vitamin-restricted diet

Micronutrients can affect birth weight directly,

had significantly higher body fat and altered lipid

indirectly, or both by their interaction with each other.

metabolism at 6 months of age, suggesting a predispo—

Deficiency in one or more micronutrients is due to

sition to insulin resistance in later life [36]. Similarly, inadequate food intake, poor dietary quality, poor in a prospective study on urban women from South

bioavailability, or a combination of these factors. Thus, India, the most notable finding was that low maternal quite often in developing countries where LBW is

vitamin B12 concentration throughout pregnancy was

prevalent, multiple micronutrient deficiencies coexist, independently associated with increased risk of IUGR

and the reductionist approach seems illogical. There

even after controlling for all possible maternal factors is no such thing as a key micronutrient and a single

[37].

micronutrient supplement would be expected to pro—

It is also true with regard to deficiencies of miner—

duce an effect only if it were the sole nutrient limitals such as iron, zinc, and calcium, which are known ing fetal growth. A systematic review on micronutri —

to have an important role in fetal growth. In a com—

ents and fetal growth shows that there is no good evi-48

parative study on women who delivered LBW babies

dence that single-micronutrient supplements lead to

(g)

69

gain

66

82

81

76

75

79

78

79

71

77

intake

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±

±

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fat

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0.05

0.01

0.01

Placental

weight

347

354

358

371

Ↄ

0.41

352

353

370

Ↄ

0.07

354

348

352

371

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weight

and

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activity,

Sub-scapular

skinfold

3.9

4.1

4.0

4.3

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4.1

4.1

4.1

4.1

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4.1

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0.48

18

at

a

weight,

serum

milk

1.8

2.0

1.9

1.7

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0.001

0.005

vegetables,

Abdominal

(cm)

28.2

28.2

28.6

29.1

Ↄ

Ↄ

28.6

28.5

28.8

0.15

0.45

28.5

28.6

28.5

28.8

0.15

0.52

pre-pregnant

measurements

for

leafy

gestation

(cm)

green

1.0

0.8

0.9

0.9

0.8

0.9

0.8

1.0

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0.8

0.9

weeks

upper a

±

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for

28

Neonatal

0.05

0.05

0.05

adjustment

at

Mid

arm

9.6

9.6

9.7

9.9

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9.7

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9.8

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0.80

9.6

9.7

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fruits

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concentration

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after

Head

(cm)

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32.9

33.2

33.3

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32.7

32.9

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48.0

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47.5

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48.1

Ↄ

0.23

47.5

47.6

47.6

48.0

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delivery,

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intake

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340

355

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gestational

maternal

Birth

(g)

2571

2601

2675

2742

Ↄ

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2598

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2721

Ↄ

0.13

2643

2618

2639

2704

Ↄ

0.14

of

and

macronutrients

and

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60

175

225

149

p

p

44

363

202

p

p

95

134

116

281

p

p

parity,

frequency

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between

SD.

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Once/wk

Alternate

Once/wk

0nce/wk

Alternate

Frequency

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Once/wk+

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days

Ↄ

Once/wk+

≥

Once/day

Never

Ↄ

Once/wk+

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days

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Relation

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milk

Circumference.

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Food

group

Green

Leafy

Vegetables,

wk

Fruits,

wk

Milk

products,

wk

a

Values

p

up

for

Section 1: Nutritional regulation and requirements for pregnancy and fetal growth Percent

Reappraisal of maternal interventions 70

NonPregnant

The current research thus underscores the impor-

Pregnant

tance of maternal nutrition in the short-term – that

is, with respect to improving birth outcome – and in

the long-term, given that fetal adaptations to maternal **35**

undernutrition increase risks of adult disease in later life. Reappraisal of maternal interventions is essential not only to improve existing interventions but

also to explore future possibilities through systematic **0**

research.

S/SE Asia

Africa

China

LAC

E Asia

First, it is necessary to investigate whether the addi-ACC/SCN, 1992

tion of a few micronutrients to existing interventions Figure 5.4 Prevalence of anemia in women aged 15 to 49 years.

with iron and folic acid is necessary to improve birth outcome. For example, vitamin A, calcium, or zinc

could be of potential interest given their association improvement in fetal growth and survival in under—

with fetal growth. Thus, well-conducted trials to deter-nourished populations. The more logical approach of mine whether there are benefits of supplementation

multiple-micronutrient supplements has been inade—

with multiple micronutrients compared with a single

quately tested [42]. Randomized control trials exam-micronutrient in populations at high risk of micronu-ining the impact of multiple vitamin and mineral trient deficiency and LBW are essential. The second

supplementation during gestation on birth weight,

important issue is that of the timing of intervention.

although scarce, have shown significant effects [44,

In rural communities in the developing world, where

45].

poor nutritional status of young girls before concep—

In view of the widespread prevalence of anemia

tion poses high risk for LBW, it is important to exam-

(Figure 5.4) and the unequivocal benefits of folic acid ine whether preconceptional nutritional supplemen-in preventing neural tube defects, the most popu-tation would yield greater effects on birth outcome.

lar maternal intervention with micronutrients that is Third, considering the limited resources available in under way in many developing countries is that of

such countries, it is worthwhile to explore the possibil-iron and folic acid. However, it cannot be denied that ity of planning food-based rather than pharmaceutical despite implementation of this maternal intervention

interventions and study their efficacy along with their over 2 decades, it has hardly improved the pregnancy

implications for health policy.

outcome in India. It is worthwhile to mention here

More detailed studies in subgroups of mothers to

that this supplementation is often given in the last 100

examine mechanisms including the effects of micronu—

days of pregnancy, although in fact it is required in trients on the maternofetal supply line, maternal

early pregnancy. Secondly, the dose of folic acid given metabolism and body composition, and adaptation to

in this intervention is high, approximately 4 times

pregnancy and infection are needed. Studies that look the requirements of a nonpregnant woman. Increas—

into interactions between micronutrients and their

ing concern has been raised for high levels of folic

bioavailability are also necessary. Finally, nutrition acid supplementation in regions where vitamin B12

intervention cannot be a permanent solution, espe—

deficiency is endemic [46]. In particular, imbalance cially in countries with limited resources. In many between folate and vitamin B12 may be associated with poor communities, improving environment, knowl—

adverse neurological effects in vulnerable sectors of the edge, and awareness through social actions would be

population such as pregnant and lactating women and

an ultimate answer to yield sustainable benefits. Thus, their infants [47]. A recent finding from the PMNS

the combined efforts of scientists, clinicians, and pol-has shown that children born to mothers with low—

icy makers in different countries are needed to eval—

est vitamin B12 but highest folate status had the most uate the relevance and appropriateness of the exist—

adipose tissue and the highest insulin resistance at

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Section 1

Nutritional regulation and requirements for pregnancy and

Chapter

fetal growth

6 **Preeclampsia**

Fergus McCarthy and Louise Kenny

Definition of preeclampsia

proposes that preeclampsia is an exaggerated form of

the inflammatory response of normal pregnancy. It

Preeclampsia is defined by the International Society

is suggested that this occurs in response to a relative

for the Study of Hypertension in Pregnancy as gesta—

increase in trophoblastic debris, which is released

tional hypertension of at least 140/90 mmHg on two

from a poorly perfused placenta. The exaggerated

separate occasions 4 or more hours apart accompanied

inflammatory response can also be triggered by a

by significant proteinuria of at least 300 mg in a 24—

normal amount of trophoblastic debris in susceptible

hour collection of urine, arising de novo after the 20th

women [7]. The second theory, the two-stage process, week of gestation in a previously normotensive woman associates the primary event for the development of

and resolving completely by the 6th postpartum week

preeclampsia appears as a failure of the second wave

[1]. It usually occurs during the second half of preg-of trophoblast invasion from 16 to 20 weeks gestation nancy and complicates 2% to 8% of pregnancies. Some

with failure to destroy the muscularis layer of the

women are considered to be at higher risk of develop—

spiral arterioles. This causes shallow endovascular

ing preeclampsia than the general female population,

cytotrophoblast invasion with enhanced inflamma—

and some of these are listed in Table 6.1. For example, tory response and endothelial cell dysfunction as key women with antiphospholipid syndrome have a risk

features in the pathogenesis of preeclampsia [8]. This approximately 9 times greater than that of the general endothelial dysfunction appears to occur as a result of

population of developing preeclampsia.

oxidative stress and is mediated by high levels of free

Implications of preeclampsia

radicals and low levels of antioxidants as supported

by the observation that markers of oxidative stress are

Preeclampsia is a major cause of maternal and perina—

present in the maternal circulation of affected women

tal mortality and morbidity worldwide, causing 15%

[9].

of all direct maternal deaths in the United Kingdom

[2] and a fivefold increase in perinatal mortality with iatrogenic prematurity being the main culprit [3]. The Confidential Enquiry into Stillbirths and Deaths in **Potential contribution by specific**

Infancy report cites one in six stillbirths as occurring

nutritional deficiencies

in pregnancies complicated by maternal hypertension

Many vitamins and food supplements have been advo-

[4]. Preeclampsia also carries implications in adult life, cated for the prevention of preeclampsia, and oth-with offspring of affected preterm pregnancies demon-ers, in excess or in deficiency, have been impli—

strating poor growth in childhood [5] and an increased cated in the pathogenesis of the disease. However, risk of hypertension, heart disease, and diabetes [6].

because the precise mechanisms underlying the etiology of preeclampsia at a cellular and molecular level

Pathogenesis of preeclampsia

are incompletely understood, it is largely unknown

The individual stages in the pathogenesis of

whether the correction of nutritional deficiencies or

preeclampsia are generally well accepted. However,

other forms of dietary manipulation may play a part

debate continues regarding the primary precipitating

in primary prevention of this disease. Similarly, it is

factor. Two theories, the two-stage process and the

not known whether dietary intervention would be

continuum theory, have emerged to explain the

most effective if commenced preconceptually or ante-

primary precipitating factor. The continuum theory

natally. In this chapter, we discuss the role of maternal

Section 1: Nutritional regulation and requirements for pregnancy and fetal growth Table 6.1 Risk factors for the development of Table 6.2 Summary of role of dietary supplements in the

preeclampsia

prevention or treatment of preeclampsia

Unadjusted relative

Role in treatment/prevention of

risk (95% confidence

Dietary agent

preeclampsia

Risk factor

interval)

Antioxidants

Reduction in relative risk of developing

Age ≥ 40 years, primiparae

1.68 (1.23–2.29)

preeclampsia, reduction of incidence of

small for gestational age but an increase

Age ≥ 40 years, multiparae

1.96 (1.34–2.87)

in the incidence of preterm labor

Family history

2.90 (1.70–4.93)

Vitamins C and E have conflicting

Nulliparity

2.91 (1.28–6.61)

evidence but do not appear to be

beneficial; their use may be associated

Multiple pregnancy

2.93 (2.04–4.21)

with adverse outcomes

Preexisting diabetes

3.56 (2.54–4.99)

L-arginine

Insufficient evidence to recommend its

use

Prepregnancy body mass

4.29 (3.52–5.49)

index ≥ 35

Calcium

Significant reduction in occurrence of

preeclampsia particularly in high-risk

Previous preeclampsia

7.19 (5.85–8.83)

groups

Antiphospholipid

9.72 (4.34–21.75)

Associated with increased risk of HELLP

syndrome

syndrome (hemolysis, elevated liver

enzymes, low platelets)

nutrition in the prevention and development of

Chinese herbal

Insufficient evidence to recommend its

medicine

use

preeclampsia.

Fish oil

No evidence of any benefit

Folic acid

Insufficient evidence to recommend its

Antioxidants

use

Antioxidants protect proteins and enzymes from oxi—

Garlic

No evidence of any benefit

dation and destruction by free radicals and help to

Iron

May worsen predisposition to

maintain cellular membrane integrity. Antioxidants

developing preeclampsia

can be categorized as either free radical scavengers that

Japanese herbal

Insufficient evidence to recommend its

trap or decompose existing free radicals, or cellular

medicine

use

and extracellular enzymes that inhibit peroxidase reac—

Magnesium

No evidence of any benefit

tions involved in the production of free radicals [10].

Multivitamin

Insufficient evidence to recommend its

Free radical scavengers include vitamin C (ascorbate),

supplementation

use

vitamin E (tocopherols), carotenoids, and glutathione.

Salt intake

No evidence of any benefit

Antioxidant enzymes include glutathione peroxidase,

Zinc

No evidence of any benefit

superoxide dismutase, and catalase, which are dependent on the presence of

cofactors such as selenium,

and lycopene, sometimes with other interventions (e.g.

zinc, and iron. Although antioxidant enzymes are

aspirin). Supplementation with any antioxidants dur—

important for intracellular defenses, nonenzymatic

ing pregnancy compared with control or placebo was

antioxidants are the major defense mechanism in the

associated with a 39% reduction in the relative risk of

extracellular compartment.

preeclampsia, which corresponds to an absolute risk

Many studies have been performed to investigate

reduction of 3%. There was also a reduction in the

the link between a variety of antioxidants and the

incidence of small-for-gestational-age infants, but a

development of preeclampsia. Many of these were of

slight increase in preterm birth. However, most of the

poor quality with inconclusive results. Therefore, a

data came from poor quality and/or quasi-randomized

Cochrane review was performed. In its final analysis,

studies. Data were insufficient to allow reliable conclu—

this included seven trials involving more than 6000

sions about the possible impact of this therapy in sub—

women and assessed the effectiveness of any antiox—

groups of high-or low-risk women or to provide guid—

idant supplement during pregnancy for prevention

ance on the optimal type and dosage of antioxidants or

of preeclampsia [11]. Supplements included various timing of supplementation.

doses and combinations of vitamin C, vitamin E, sele—

Vitamins C and E have been studied because

nium, halibut liver oil (containing vitamin A), fish oil,

of their perceived function as antioxidants. In one

randomized trial, vitamin C (1000 mg/day) and vita—

antioxidant supplementation in pregnancy. Therefore,

min E (400 IU/day) were administered to women at

at present, antioxidant supplementation in the form of

high risk of developing preeclampsia during the sec—

vitamin C and vitamin E cannot be recommended for

ond and third trimesters [12]. Vitamin supplementa-the prevention or treatment of preeclampsia.

tion was associated with a significant reduction in the

frequency of preeclampsia. However, subsequent tri—

Arginine

als have not confirmed these findings. A larger, mul—

Arginine is an alpha amino acid that is synthesized

ticenter trial in a diverse group of women at high risk

by adults through the urea cycle. Arginine is the

of developing preeclampsia, conducted by the inves—

immediate precursor of nitrous oxide, urea, ornithine,

tigators of the original study, found that the inci—

and agmatine. Nitrous oxide is a potent vasodila—

dence of preeclampsia was similar for women given

tor; therefore, arginine supplementation has been sug—

vitamin C and E supplementation and those given

gested as a potential treatment in a condition in

placebo [13]. This study also reported that the num-which vasodilatation may be beneficial. Administra-ber of low birth weight neonates was slightly higher in tion of organic nitrates or L-arginine has been shown

treated women. This may have been related to a trend

to improve uterine-placental circulation and to lower

toward slightly earlier onset and more severe disease

maternal blood pressure [19–22]. A recent pilot study in treated patients. Post hoc analysis showed that vita-by Facchinetti *et al.* [23] shows promising results in min supplementation was associated with increased prolonging the latent period to the development of

frequency of gestational hypertension and stillbirth.

preeclampsia in patients with gestational hyperten—

Another multicenter trial randomly assigned nulli—

sion by means of arginine supplementation. How—

parous women without medical or obstetrical com—

ever, this benefit needs to be confirmed in larger

plications to receive daily supplementation with vita—

studies with adequate power to evaluate the effec—

min C plus vitamin E or placebo from the sec—

tiveness of L-arginine in preventing the development

ond trimester until delivery [14]. The incidence of to preeclampsia. Currently, arginine supplementation preeclampsia was similar for both groups. There were

cannot be recommended for the prevention or treat—

no significant differences in the incidence of small-for—

ment of preeclampsia [24].

gestational-age neonates, death/serious neonatal complications, or preterm birth. The difference in prevalence of preeclampsia between these two trials may

Calcium

be attributed to differences in the populations studied.

The relationship between calcium intake and hyper—

Certainly it seems that antioxidant supplementation

tension in pregnancy was first described in 1980, when

does not prevent preeclampsia. Furthermore, there is a

epidemiological studies suggested that women who

possibility that the therapy increases the risk of adverse lived in areas with high dietary calcium intake had a

effects in women with specific risk factors for the

lower incidence of preeclampsia. A Cochrane system—

disease.

atic review including 12 studies of more than 15 000

Two studies have addressed the issue of whether

women compared the use of at least 1 g of calcium

antioxidants alter the course of established preeclamp—

daily during pregnancy with placebo [25]. Preeclampsia [15, 16]. Neither reported a clinical benefit.

sia was significantly reduced with calcium supplemen—

A recent systematic review of trials evaluating vita—

tation compared with placebo. A similar effect was

min E supplementation in a variety of clinical settings

observed in nonproteinuric hypertension. The effect

[17] demonstrated harmful effects associated with was greatest for women at high risk of developing supplementation. A recently published case-control

preeclampsia and for those with low baseline calcium

study investigated the association between maternal

intake. Calcium supplementation was also associated

dietary and supplement intake of the antioxidants

with a significant reduction in the incidence of mater—

vitamin E, retinol, and congenital heart defects [18].

nal death or serious morbidity, but somewhat perplex—

This study demonstrated an association between high

ingly, it increased the incidence of HELLP syndrome.

maternal vitamin E intake by diet and supplements

HELLP syndrome refers to a clinical syndrome charac—

and an increased risk of congenital heart disease in

terized by hemolysis, elevated liver enzymes, and low

the mother’s offspring. These findings highlight the

platelets that may occur in pregnancy. It is thought

55

need for controlled evaluation of vitamin E and other

to represent a variant of preeclampsia. The benefit

Section 1: Nutritional regulation and requirements for pregnancy and fetal growth from calcium supplementation appears to be mater-analysis of these trials also failed to show a reduction nal as there was no effect on the risk of preterm

in the risk of preeclampsia [34].

birth or perinatal death. There were no reports of

adverse events related to calcium supplementation but

long-term follow-up was minimal. Overall, the benefits of less preeclampsia, fewer maternal deaths, and

Folic acid

reduced severe morbidity support the use of calcium

Homocysteine has been reported to be increased

supplementation during pregnancy for women with

in the plasma of women who subsequently develop

low dietary intake of calcium.

preeclampsia. Elevated homocysteine levels may damage the lining of blood

vessels resulting in the signs

and symptoms of preeclampsia. Folic acid supple—

Chinese herbal medicine

mentation has been studied in women with hyper—

Traditional Chinese medicine is a theoretical and

homocysteinemia because homocysteine levels have

methodological system that incorporates concepts of

been weakly and negatively correlated with plasma

cause, diagnosis, and treatment. Several traditional

folate concentrations. Leeda *et al.* [35] supplemented Chinese medicines are thought to protect the mater-a high-risk group of women with hyperhomocys-nal spleen, liver, and kidneys in preeclampsia by teinemia and a history of previous preeclampsia or

encouraging vasodilatation, increasing blood flow,

intrauterine growth restriction with 5 mg folic acid and

and decreasing platelet aggregation. Some of these

250 mg of vitamin B6. The supplementation resulted

medicines have been reported to be effective in the

in a normalized methionine loading test in all patients

treatment of preeclampsia [26]. However, in a sys-in the study and showed a favorable perinatal out-tematic Cochrane review, no appropriate good-quality come. The study had very small numbers and was

randomized controlled trials were found for analy—

not randomized to placebo. Folic acid may have a

sis [27]. Therefore, Chinese herbal medicine cannot role to play in this high-risk group, but in the gen-be recommended for the prevention or treatment of eral population, it is not known whether folic acid

preeclampsia.

has a role to play in the prevention or treatment of

preeclampsia.

Fish oil

It has been proposed that fish oil supplements may

have a variety of protective vascular effects includ—

Garlic

ing reductions in systemic blood pressure and in

Garlic is part of the Allium or onion, family. The sug—

the incidence of preeclampsia and pregnancy-induced

gestions that garlic may lower blood pressure, reduce

hypertension [28, 29]. One randomized double-blind oxidative stress, inhibit lipid oxidation, and/or inhibit placebo controlled trial randomized 253 pregnant

platelet aggregation have led to the hypothesis that

women at high risk of developing proteinuric or non—

garlic may have a role in prevention of preeclamp—

proteinuric pregnancy-induced hypertension or asym—

sia [36–38]. Experimental studies have demonstrated metrical intrauterine growth retardation to 2.7 g of that garlic may also increase the production of

nitric

MaxEpa daily (1.62 g of eicosapentaenoic acid and 1.08

oxide [39], which is itself a platelet inhibitor and g of docosahexaenoic acid) or placebo. There was no vasodilator. A Cochrane review looked at the use of

difference in an intention-to-treat analysis between the

garlic for preventing preeclampsia and its complica—

placebo and active treatment groups for occurrence of

tions [40]. Only one trial of 100 women met inclusion any of the primary outcomes [30]. A second prospec-criteria, and it showed no difference between dried tive trial enrolled 386 pregnant women with a his—

garlic and placebo in the prevention of preeclamp—

tory of pregnancy-induced hypertension in a previous

sia [41]. There is insufficient evidence to recommend pregnancy and randomly assigned them to a fish oil or increased garlic intake for preventing preeclampsia

olive oil supplement, beginning after 16 weeks of gesand its complications. However, because there are now

tation [31]. These and two subsequent trials [32, 33]

many varieties of garlic available and there is a lack

found that fish oil supplementation had no effect on

of appropriately powered studies, further research is

the incidence or development of hypertension. Meta—

warranted.

Chapter 6: Preeclampsia

Iron

tation. However, of the seven studies included in the

systematic analysis, only one study met the prespec—

The placental ischemia and malperfused placenta that

ified criteria for a high-quality trial. This one high—

occur in preeclampsia result in the production of free

quality study randomized 400 normotensive primi—

radicals, which may cause oxidative stress [8]. These gravid women aged 13 to 25 years to receive 365 mg free radicals such as superoxide and hydrogen per—

elemental magnesium or placebo daily from 13 to 24

oxide are unlikely to initiate cellular damage directly.

weeks gestation. The authors concluded that the poor

However, in the presence of metal ions, particularly

quality of many of the trials was likely to have resulted

iron and copper, they can generate hydroxyl radical,

in a bias favoring magnesium supplementation, but

which can result in endothelial cell damage [42, 43].

there is not enough high-quality evidence to show

Iron is already present in large amounts in the pla—

that dietary magnesium supplementation during preg—

centa, and levels may further increase in the ischemic

nancy is beneficial in reducing the incidence or sever—

placenta by destruction of red blood cells from throm—

ity of preeclampsia. There were also no differences

botic, necrotic, and hemorrhagic areas [44]. No trials between the magnesium and placebo groups for the have demonstrated that the routine use of iron supple—

frequency of preterm birth (Ↄ37 weeks), gestational

mentation in pregnancy can prevent the development

age at birth, birth weight, small for gestational age, the of preeclampsia. Iron supplementation, unlike many of

frequency of admission to a neonatal unit, miscarriage,

the other dietary components discussed in this chap—

and neonatal death [48].

ter, may also have a detrimental effect when used in

excess in pregnancy by promoting oxidative stress by

decreasing serum antioxidant capacity.

Multiple micronutrient supplementations

Japanese herbal medicine

Micronutrients are vitamins and minerals required in

In Japan, certain traditional herbal medicines (Kampo

minute amounts for normal functioning, growth, and

medicines) are used clinically with standardized

development. Micronutrients include vitamin A, zinc,

quantities and quality of ingredients. One of these

iron, and beta carotene. The resulting micronutrient

medicines, Tokishakuyakusan (TS), is used to alle—

deficiencies are exacerbated in pregnancy, leading to

viate symptoms of menopause and as a tocolytic in

potentially adverse effects on the mother such as ane—

the treatment of preterm labor. One animal study

mia, hypertension, complications of labor, and death.

performed investigated the effect of TS on pregnant

A Cochrane review involving nine trials and more than

rats in which a preeclampsia-like syndrome had been

15 000 women showed insufficient data to demonstrate

induced [45]. The authors concluded that TS may have a reduction in the development of preeclampsia by a beneficial effect in preeclampsia, but further studies

routine use of micronutrients [49].

are needed.

Magnesium

Salt intake

Magnesium is one of the essential minerals required

Controlled salt intake has long been recommended for

by humans in relatively large amounts. Magnesium

the control of essential hypertension. On this basis,

works with many enzymes to regulate body tempera—

salt restriction was widely recommended during preg—

ture and synthesize proteins as well as to maintain elec—

nancy for the prevention and treatment of preeclamp—

trical potentials in nerves and muscle membranes. The

sia. However, the literature has mixed opinions, and

MAGPIE (Magnesium Sulphate for the Treatment of

at one stage in the 1960s, high salt intake was rec—

Preeclampsia) trial demonstrated the importance of

ommended to prevent preeclampsia [50]. Duley *et al.*

magnesium in the treatment of preeclampsia and the

[51] performed a Cochrane review that included two prevention of eclampsia [46]. Many women, especially trials involving 603 women. Neither trial proved a those from disadvantaged backgrounds, have intakes

reduced incidence of preeclampsia in the presence

of magnesium below average. Makrides and Crowther

of salt [52]. Therefore, in the absence of further evi-

[47] systematically reviewed the use of magnesium dence, salt intake during

pregnancy remains a personal **57**

supplementation in pregnancy before 25 weeks ges—

preference [53].

Section 1: Nutritional regulation and requirements for pregnancy and fetal growth Zinc during pregnancy may not be without risks with several observational studies linking exercise during preg—

Zinc is one of the mediators of the antioxidant enzymes

nancy with small-for-gestational-age babies, preterm

such as glutathione peroxidase, superoxide dismutase,

birth, and maternal injury [62, 63]. Two studies met and catalase. A low maternal serum zinc concentra-the requirements for a Cochrane review [64]. However, tion has been reported in pregnancies complicated by these trials had small numbers and were unable to pro—

preeclampsia [54, 55], and it has been suggested that vide reliable conclusions regarding the role of exercise the incidence of preeclampsia may be reduced by zinc

in the prevention of preeclampsia [65].

supplementation [56]. One double-blind randomized control trial investigated the effect of zinc supplementation on a healthy middle-class population of more Vegans

than 1000 women and concluded that zinc supplemen—

Veganism is a philosophy and lifestyle that seeks to

tation does not appear to have any role in the preven—

exclude the use of animal derived products for food,

tion or treatment of preeclampsia [57]. It may have a clothing, or any other purpose. Vegans do not use or role to play in improving birth weight and

preventing

consume animal products of any kind. Carter *et al*. [66]

prematurity in populations at high risk of poor preg—

examined the incidence of preeclampsia and repro—

nancy outcomes.

ductive outcomes in a community of vegan mothers.

The study included 775 women, 240 of whom were

The role of diet and lifestyle factors

primigravidas. This retrospective observational study

revealed only one case of preeclampsia occurring in

Rest

this cohort of women suggesting that a vegan diet, a

diet that is low in arachadonic acid, may be protective

Restriction of activity and prolonged resting have tra—

against the development of preeclampsia. Other possi—

ditionally been advocated for the prevention and treat—

ble explanations for the low incidence of preeclampsia

ment of many of the ailments of pregnancy, includin this population include the retrospective nature of

ing the prevention and treatment of hypertension [58].

the study, which may have resulted in bias, low levels

This was based on a belief that exercise may reduce

of smoking and stress, a “healthy” diet, and high levels

uteroplacental blood flow and therefore rest would

of aerobic exercise.

increase it. Women with preeclampsia suffer from

reduced uteroplacental blood, and therefore it was

Obesity

hypothesized that rest might prevent or reduce the

severity of preeclampsia. Two studies met inclusion

An association between obesity and hypertensive

criteria for a Cochrane review [59, 60]. These two stud-disorders during pregnancy has been consistently ies, although included, were themselves substandard,

reported. In particular, maternal weight and body

raising more questions than they answered. There is

mass index (BMI) are independent risk factors for

insufficient evidence to support recommending rest or

preeclampsia, as well as other hypertensive disor—

reduced activity to women for preventing preeclamp—

ders [67–69]. A review of 13 cohort studies compris-sia and its complications [61]. It is also unclear whether ing nearly 1.4 million women found that the risk of rest and the resulting immobilization may predis—

preeclampsia doubled with each 5 to 7 kg/m2 increase

pose pregnant women to increased risks of throm—

in prepregnancy BMI [69]. This relation persisted boembolic disease in the hypercoagulable setting of in studies that excluded women with chronic hyper—

pregnancy.

tension, diabetes mellitus, or multiple gestations, or

after adjustment for other confounders. The mechanism whereby obesity imparts an increased risk

Exercise

for preeclampsia is not known. Current hypotheses

The evidence linking the promotion of regular exer—

suggest that the pathophysiological changes associ—

cise and a reduction in the risk of hypertension in

ated with obesity-related cardiovascular risk, such

the nonpregnant person is well established. However,

as insulin resistance, hyperlipidemia, and subclinical

it remains unclear whether the promotion of exercise

inflammation, are also responsible for the increased

in a pregnant woman will reduce her risk of devel—

incidence of preeclampsia in obese pregnant women

oping or reduce the severity of preeclampsia. Exercise

[70–72].

Chapter 6: Preeclampsia

What dietary advice can be given and

effects of calcium supplementation at a community

how does this relate to those with a

level.

genetic predisposition?

Key clinical points

The search for dietary supplements that may prevent

r Preeclampsia is a common condition

or treat preeclampsia continues, and currently there

complicating 2% to 8% of pregnancies.

is no good evidence to support the routine use of

r Preeclampsia is a leading cause of severe obstetric

dietary supplements in the prevention and treatment

morbidity and mortality for both mother and

of preeclampsia in a low-risk antenatal population.

fetus throughout the world.

Those patients at high risk of developing preeclampsia

r Preeclampsia is associated with a fivefold increase

should be considered on an individual basis. Achievin perinatal mortality and

has medical

ing an ideal BMI relationship between a person’s height

implications such as the development of diabetes

and weight by weight loss before conception may be

late into adult life.

the most prudent advice in many patients. Calcium

r It is believed to be the result of an exaggerated

supplementation may be considered in women at high

form of the inflammatory response of normal

risk for developing preeclampsia but only after poten—

pregnancy.

tial risks are discussed. Further dietary supplementa—

r The mechanisms underlying this etiology are

tion is not recommended outside of the setting of a

poorly understood, and therefore it is difficult to

clinical trial, and patients should be made aware that

speculate whether the correction of nutritional

dietary supplementation may have adverse effects on

deficiencies may play a part in primary

the mother or fetus.

prevention.

r Many dietary agents and lifestyle factors have

Potential future research

been implicated in its occurrence. However,

Unfortunately, more than anything, this chapter high—

good-quality randomized trials comparing these

lights the significant lack of quality studies from which

agents against placebo are generally not available.

to draw conclusions regarding the role of nutrition in

It is therefore not possible to recommend the use

the prevention or treatment of preeclampsia. Further

of many of these agents in the prevention and

research is needed to clarify whether potential health

treatment of preeclampsia.

benefits are specific to particular preparations, con—

r Some dietary interventions used such as iron

stituents, or doses. Further trials should be large and

supplementation may be detrimental and further

should collect information about perinatal mortality

predispose women to developing preeclampsia.

and morbidity as well as maternal mortality and morr Dietary advice with the aim of achieving an ideal

bidity associated with any intervention. A particularly

BMI is one of the few dietary interventions known

important topic appears to be that of determining the

to reduce the risk of developing preeclampsia.

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Section 2

Nutritional regulation and requirements for lactation and

Chapter

infant growth

7 **Macronutrientsforlactationand**

infant growth

Thibault Senterre and Jacques Rigo

Mammary growth

mammary gland and ducts. Colostrum is progressively

replaced by newly secreted milk, called transitional

Pregnancy results in many transformations and adap—

milk. The initial physiological changes on the first

tations of the woman’s body that continue after deliv—

day after delivery are independent of suckling or milk

ery. Each species has developed its own strategies

expression, but breastfeeding frequency on the sec—

to meet the nutritional needs of its offspring. Sys—

ond day of life is positively correlated with milk volume

temic hormones, including pituitary prolactin, ovar—

on Day 5. Thereafter, milk volume depends on infant

ian estrogen and progesterone, placental lactogen, and

demand, and potential milk available at each feeding

metabolic hormones, influence breast development.

is comparable. The maintenance of established milk

Initial changes observed during pregnancy include an

secretion is mainly dependent on the hypothalamic—

increase in ductal branching and the formation of alve—

pituitary axis, which regulates prolactin and ocytocin

olar buds. Expansion of alveolar buds occurs to form

secretion secondary to suckling stimulation [1, 4, 5].

clusters of lobuloalveolar units, followed by the differ—
Initial volumes of colostrum vary between 2 and 20
entiation of these structures into presecretory struc—
ml per feeding. Two to three days after delivery, transi—
tures [1–3].
tional milk appears and is characterized by an increase
Lactogenesis begins during pregnancy and secre—
in volume and by major changes in composition until
tory material accumulates in the acini from the third
the second week of life. Immunoglobulins and pro—
month of gestation. This prepartum milk is mainly
tein content decrease, whereas fat and lactose content
formed of proteins and glycoproteins. Large lipid
increase the caloric content. Milk volume is associ—
droplets are also present in alveolar cells and in lumi—
ated with lactose secretion and water dilution. Volume
nal spaces. After delivery, lactogenesis is stimulated
of milk increases from less than 100 ml/day on the
by a fall in plasma progesterone, while prolactin level
first day to about 600 ml/day after 96 hours. The mean
remains high. This phenomenon is independent of

amount of milk produced by mothers from developed
suckling and declines after a few days if the breast is
countries is quite similar to women from developing
not stimulated. Histological examination of the mam—
countries. Parity has a positive influence on the onset
mary gland during lactation reveals prominent lumi—
of milk volume. Milk production is stable during the
nal structures and ducts. Few adipocytes are visible,
first months of lactation, but there is a wide range
reflecting their delipidation rather than a decrease in
of milk intake among healthy breastfed term infants,
their number. Change in the size and cellular distribu—
averaging 750 to 800 ml per day but ranging from 450
tion of lipid droplets is the more obvious histological
to 1200 ml/day because of infant demands (Table 7.1).
transition from pregnancy to lactation [1, 3, 4].
If exclusive breastfeeding is continued after 6 months
of age, milk production continues to increase. When

Human milk production and

complementary feedings are introduced, milk production decreases because of the infant's demand reg-

composition

ulation and is usually between 400 and 600 ml in

There is remarkable similarity in women’s milk pro—

developed countries and between 600 and 700 ml

duction throughout the world, independent of lifestyle

in developing countries. Several studies reported a

and nutritional status. Colostrum is the first milk pro—

potential capacity of milk production up to 3 to 3.5

duced just after delivery; this thick and yellow milk

l/day. Any factor influencing frequency, intensity, or

contains a mixture of residual materials present in

duration of suckling influences the volume. Exercise,

Section 2: Nutritional regulation and requirements for lactation and infant growth Table 7.1 Human milk (HM) composition (first 6 months) tose and triglycerides. A lot of oligosaccharides have

Volume

750–800 ml/day

(range, 450–1200 ml/day)

been identified in human milk. They are implicated in

many functional aspects of human milk [8, 12, 13].

Energy

2800 kj/l

670 kcal/L

Most proteins are specific of milk secretions. They

Fats

37–40 g/l

50%–55% of HM energy

are synthesized from free amino acids in the secre—

Carbohydrates

70–74 g/l

40%–45% of HM energy

tary cells of mammary glands. Human milk proteins

Proteins

8–12 g/l

5%–6% of HM energy

are mainly composed by casein and whey proteins.

The term casein includes a group of milk-specific pro—

manual labor, and losing weight do not usually alter an

teins characterized by ester-bound phosphate, high

established milk volume secretion because of energy—

in proline content, and with low solubility at pH 4–

sparing adaptations. Milk volume diminishes only in
5. Caseins form particles or micelles that are com—
extreme malnutrition or severe dehydration. In fact,
plexes of calcium caseinate and calcium-phosphate,
lactose content is the main regulator of osmolality and
which enhance calcium/phosphorus absorption and
milk volume is related to lactose synthesis, which is
biodisponibililty. Concentration of protein in human
very stable [1, 5–7].
milk and whey protein:casein ratio vary with lactation.
Energy density of human milk is related to pro—
Human milk proteins concentrations based on nitro—
tein, fat, and carbohydrate contents. In well-nourished
gen measures decline from approximately 2–3 g/dl in
populations, milk fats average about 37 to 40 g/l and
colostrum to about 1.3–1.5 g/dl on Day 10 after deliv—
contribute to half or more of the total energy: milk
ery, 1.0–1.2 g/l at 1 month, and 0.8–0.9 g/dl thereafter.
carbohydrates average approximately 70 to 74 g/l and
The whey protein:casein ratio changes from 90:10 in
40% to 45% of total energy, and milk proteins average

early milk to 60:40 in mature milk and 50:50 in late

approximately 8 to 12 g/l and only 5% to 6% of total

lactation. Nonprotein nitrogen accounts for approx—

energy (Table 7.1). Even if milk protein concentration imately 25% of total nitrogen in human milk (rang-decreases with postnatal age, these have relatively lit-ing from 18% to 30%). Nonprotein nitrogen is not tle impact on global milk energy density. According to

included in the true protein content, which is equiv—

various studies, energy density in human milk varies

alent to protein as determined by amino acid analy—

from 255 kJ/dl (61 kcal/dl) to 310 kJ/dl (74 kcal/dl).

sis. True protein content is equivalent to total nitro—

The mean metabolizable energy content generally used

gen minus nonprotein nitrogen, multiplied by 6.25.

for human milk is 280 kJ/dl (67 kcal/dl; Table 7.1)

Urea represents 30% to 50% of the nonprotein nitro-

[5, 8–11].

gen fraction and increases from colostrum to mature

Milk fat concentration, and thus, energy density,

milk. Urea and the remaining components of nonpro—

varies both within a feed (hind milk is higher in fat

tein nitrogen serve partially as a nitrogen pool avail—

than fore milk) and during a 24-hour period (depend—
able for nonessential amino acid synthesis but also
ing on diet, on meals, and thus on populations).
have many other functions (hormones, growth factors)
Data from different populations indicate that milk fat
[8, 13, 14].
concentration is positively correlated with body fat—
Human milk fat content is the main source of
ness. However, this may not have a strong impact on
energy and its most variable constituent. Fat content
total milk energy intake by infants allowed to nurse
is low in colostrum and increases from 2% to 5%
on demand because mean energy intake is the main
in mature milk. Prepartum secretions contain high
determinant of volume intake. Thus, low energy den—
amounts of membrane components, such as phospho—
sity may be compensated for by a higher volume
lipids, cholesterol, and cholesteryl esters that decrease
intake [9–11].
from colostrum to mature milk. Cholesterol and phos—
Lactose is the principal carbohydrate of human

pholipid content decreases during the first week to sta—
milk and is the second major component of human
bilize at approximately 10 to 20 mg/dl. Fat content
milk after water. Its concentration is stable. Human
increases during feeding and changes over a 24-hour
milk is isotonic with plasma, and 60% to 70% of
period as well as through lactation (diminishing after
osmotic pressure is due to lactose. Lactose is synthe—
6 months). Maternal body fat proportion influences
sized by the mammary gland and is constant through—
lipid concentration in human milk. Higher fat content
out the day between 6.2 and 7.2 g/dl. Oligosaccharides
has been observed in well-nourished women, espe-

are the third largest solid constituent of milk after lac—
cially in cases of higher weight gain during pregnancy.

 Primiparous women have more fat content than mul—

Table 7.2 Infant requirements during the first year of

tiparous women [8, 15].

life (World Health Organization)

Human milk lipids consist of emulsified globules

Energy

1st month

460 kJ (110 kcal) *kg*day

in the aqueous phase. The main lipids are triacyl—

6th month

339 kJ (81 kcal) *kg*day

glycerol, phospholipids, and their fatty acids. Triglyc—

12th month

334 kJ (80 kcal) *kg*day

erides constitute 98% of human milk fat and are

Protein

1st month

1.77 g*kg*day

the third major constituent after water and lactose.

Oleic acid is the predominant fatty acid (35%), and

6th month

1.14 g*kg*day

its concentration depends on vegetable oil consump—

12th month

0.95 g*kg*day

tion. The second fatty acid is palmitic acid (22%),

which increases in cases of low caloric intake. Short—

life, lowering to 339 kJ*kg*day (81 kcal*kg*day) during chain fatty acids are mainly synthesized in the mam—

the 6th month, tending to plateau until the 12th month

mary glands, and medium-chain fatty acids come from

(Table 7.2). This decrease in energy requirements is adipocytes. Long-chain polyunsaturated fatty acids related to the decreased energy deposition for growth

(LCPUFA) are derived from blood plasma and thus

from 40% of total energy requirements at 1 month to

are more dependent on maternal diet. Concentrations

3% at 12 months. These upgraded estimates are 10%

decrease during lactation and vary greatly according

to 32% lower than the previous recommendations [14,

to populations and studies: 10% to 18% for linoleic

21].

acid (LA; C18:2n6), 0.4% to 1.3% for alpha-linolenic

Infants' protein requirements can be defined as the

acid (ALA; C18:3n3), 0.4% to 0.8% for arachidonic

minimum intake that will allow nitrogen equilibrium

acid (ARA; C20:4n6), and 0.2% to 0.5% for docosahex—

at an appropriate body composition during energy bal—

aenoic acid (DHA; C22:6n3). N-6 and n-3 fatty acids
ance at moderate physical activity, in addition to the
are essential components of the phospholipids of cell
needs associated with the deposition of tissues con—
membranes. They are critical for fluidity, permeability,
sistent with good health. The composition of human
and activity of membrane-bound enzymes and recep—
milk provides the model for estimated total protein
tors. The Western diet is progressively becoming defi—
and essential amino acid requirements during infancy,
cient in n-3 fatty acids, and consequently so is maternal
taking into account the utilization of a portion of its
milk. Trans fatty acids are also present in milk, depend—
nonprotein nitrogen fraction. After 6 months, estima—
ing on mother’s diet and fat depot [8, 15–18].
tion of the protein requirements derives from a facto—
Preterm infants are usually unable to be breast—
rial approach, considering maintenance, growth depo—
fed naturally. A breast pump is used to express milk
sition, and efficiency of use. Recent reassessments of
before administration. A sterile technique is neces—

estimated requirements are 10% to 25% lower than

sary to avoid contamination, but milk pasteurization

previous ones and decrease from 1.77 g*kg*day at 1

is frequently required. Mothers who deliver prema—

month to 1.14 g*kg*day at 6 months, tending to plateau turely have higher milk nitrogen content and vari—

until 12 months [14, 22, 23] (Table 7.2).

able fat composition. In addition, some components of

Dietary fats are the main source of infants' energy,

milk, such as fat, are lost during collection and storage.

provide essential fatty acids, and facilitate the absorp—

Human milk fortification is necessary to meet the high

tion of fat-soluble vitamins. During the first 6 months

requirements of preterm infants [19, 20].

of life, an infant accumulates 1300 to 1600 g of fats.

Lipids are structural components of all tissues and

are indispensable for cell and plasma membrane syn-

Infant nutritional requirements

thesis. The brain, retina, and other neural tissues are

Infants' energy requirements are defined as the

particularly rich in LCPUFA, especially DHA. Choles—

amount of food energy necessary to balance total

terol is an essential component of all membranes and

energy expenditure at a normal level of activity and

is required for growth, replication, and maintenance.

to support and maintain growth and development

Breastfeeding induces higher plasma cholesterol

consistent with long-term health. Total infant energy

in infants than formulas, and some studies suggest

requirements increase with growth but decrease with

that it may protect against hypercholesterolemia

age if adjusted for body weight. They correspond to 460

in later life. The quality of dietary lipid supply in

kJ*kg*day (110 kcal*kg*day) during the 1st month of early childhood is a major determinant of growth,

 development, and long-term health. N-6 and n-3

agents present in the mother’s and postnatal infant’s

LCPUFA are derived from LA and ALA, respectively,

environment. The immune system protects the infant

by the same competitive enzymatic pathway, including

against pathogenic organisms, and highly complex

desaturations and elongations. LA and ALA are also pathways of recognition, response, elimination, and precursors for eicosanoid production (prostaglandins, memory have evolved to fulfill this role. The immune prostacyclins, thromboxanes, and leukotrienes). system also acts to ensure self-tolerance but also tol— These autocrine and paracrine mediators are erance to food, environmental components, and com— powerful regulators of numerous cell and tissue mensal bacteria. Any perturbations of these functions functions [16, 18, 24, 25]. may lead to infectious or inflammatory diseases [13, DHA is the most abundant n-3 fatty acid in the 32, 33]. mammalian brain. Neuronal membranes and retinal The intestine is sterile at birth, and rapid coloniza— photoreceptor cells receive most of their phospholipid tion occurs after delivery. Maternal gut flora, deliv—

DHA from the diet. Several studies suggest that DHA
ery environment, and diet are the major determinants
status in early infancy is positively related to visual
of initial intestinal flora in newborns. A specificity of
acuity and neurodevelopmental outcomes. Cerebro—
human milk is to select a flora rich in Lactobacillus and
cortical gray matter concentration of DHA in infants
bifidobacteria. Recent studies suggest that appropriate
depends on their diet supplies. Breastfed infants accu—
flora promote gut maturation and the gut-associated
mulate more DHA than formula-fed infants who are
immune system. Human milk oligosaccharides, high
not consuming dietary DHA. ALA is the precursor
lactose content, milk immunological functions, and
of DHA, but its synthesis may be limited by enzyme
other properties of human milk are the main factors
insufficiency or by enzyme competition due to an
influencing the breastfed infant's flora [12, 13, 32].
excess of n-6 fatty acids. In addition, LCPUFA synthe—
Over the past several decades, the incidence of
sis appears to decrease during the first year of life. Even atopic diseases has

increased dramatically. Environ—

in breastfed infants, DHA tissue content decreases

mental factors, including early infant nutrition, may

progressively after 6 months, when complementary

influence their development. For infants at high risk

feeding is introduced, because of its low content of

of developing atopy, there is evidence that exclusive

LCPUFA. This may lead to insufficient DHA intakes.

breastfeeding for at least 4 months prevents or delays

Therefore, especially in developing countries, breast

the occurrence of atopic dermatitis, cow's milk allergy,

milk as a source of essential fatty acids is important

and wheezing in early childhood. Epidemiologic stud—

until the end of the second year of life [16, 26–31].

ies have also suggested that early exposure to certain nutrients, including LCPUFA, may be protec-

Differences between breastfed

tive against immune anomalies. Relative intake of LA,

the n-6 LCPUFA precursor, has increased progres-

infants and formula-fed infants

sively in Western diets, suggesting a positive rela—

Human milk is markedly different from cow’s milk.

tionship between the n-6 LCPUFA supplies and the

The infant response to human milk and formula

prevalence of allergic diseases via enhanced ARA and

differs with respect to endocrine, gastrointestinal,

prostaglandin E2 production [16, 34, 35].

immune, renal, and metabolic functions. Immuno—

The available evidence suggests that breastfeeding

logical and anti-infectious proprieties of human milk

may have other long-term benefits. Infants who were

are of major importance compared with formulas.

breastfed experience lower mean blood pressure and

They are related to its cellular composition, with liv—

lower total cholesterol in adulthood, as well as higher

ing leukocytes, and to many soluble proteins such

performance in intelligence tests. Furthermore, the

as lysozyme, nucleotides, glutamine, and transferrin.

prevalence of overweight/obesity and Type II diabetes

Lactating mammary glands are part of an integrated

is lower among breastfed infants. These effects are sta—

mucosal immune system with local production of antitistically significant even

after adjustment for various

bodies, mainly consisting of secretory immunoglob—

confounding factors, but for some outcomes, the mag—

ulin A. These antibodies reflect antigenic stimulation

nitude is relatively modest. The protein:energy ratio

of mucosal-associated lymphoid tissue by common

of human milk is low compared with infant formu—

intestinal and respiratory pathogens. Antibodies in

las. It seems that a higher protein:energy ratio may be

breast milk are thus highly targeted against infectious

responsible for the accelerated growth of formula-fed infants compared with breastfed infants during the

Table 7.3 Maternal nutritional recommendation during

first year of life, which is believed to induce metabolic

lactation

imprinting with adverse later consequences of formula

Fluid

Ad libitum

feeding [13, 36–39].

Energy

+ 2100 kJ (500 kcal) /day (0–6 months)

Exclusive breastfeeding is recommended until

+ 1900 kJ (460 kcal) /day (C6 months)

6 months of age, when complementary feeding should

Protein

+ 19 g/day (0–6 months)

be introduced. Industrial interests conduct many studies to improve formulas to replicate breast milk more

+ 12.5 g/day (C6 months)

closely. Therefore, it is important to promote the use of

Lipid

+ 200 mg/day docosahexaenoic acid (fish

twice a week)

the most innovative formulas for infants when breastfeeding is not possible [33, 36, 39–41].

High risk of

No specific prevention

atopy

Postpartum

Spontaneous normal loss of 0.5–1.0

Key clinical messages

weight loss

kg/month in well-nourished mother; dietary

r

restriction not recommended

Breastfeeding during the first hours and days

after delivery improves efficiency and

persistence of breastfeeding.

The energy requirements of a lactating woman are

r Breastfeeding must be adapted according to

defined as the level of energy intake from food that

the infant’s demand.

will balance the energy expenditure needed to main—

r Exclusive breastfeeding is recommended until

tain her body weight and composition, level of physi—

6 months of age, when complementary feeding

cal activity, and breast-milk production to ensure good

should be introduced.

health for her and her child and that will allow her

r Industry is improving formulas to replicate

to perform economically necessary and socially desir—

breast milk more closely. It is important to

able activities. Energy cost of lactation is determined

promote the use of the most innovative

by the energy content of milk produced and secreted

formulas when breastfeeding is not possible.

and the efficiency of the conversion of dietary energy

for milk synthesis. For exclusive breastfeeding during the first 6 months after delivery, the total mean

Maternal needs related to lactation

energy cost could be estimated as follows: 800 ml

Milk composition is sensitive to maternal factors, such

milk/day × 280 kJ/dl *0.80 for efficiency = 2800 kJ*day as body composition, diet, and parity. Food supple-

(675 kcal/day). After 6 months, during complemen—

mentation during lactation in areas of high malnutri—

tary feeding, human milk production is approximately

tion has generally little, if any, impact on milk vol—

550 ml per day, and the energy cost decreases to 1900

ume, but it improves maternal health. Throughout the

kJ/day (460 kcal/day) [9–11].

world, women usually produce adequate and abundant

Fat and other nutrients are stored during preg—

milk, even when they have inadequate diets. When

nancy and may cover in part the additional energy

milk energy density is low, infants adapt their suckling

needs during the first months of lactation. Postpar—

behavior to increase volume intake to maintain ade—

tum weight loss is usually highest in the first 3 months

quate total energy intake [1, 5].

and is considered by mothers to be an advantage of

Lactating mothers usually describe an increase in

breastfeeding compared with formula feeding. Poten—

thirst and so adapt their fluid intake during lactatial energy mobilization during lactation depends on

tion. However, fluid intake has no positive influence

weight gain during gestation and nutritional status

on milk volume. In all infants, water requirements are

of the mother. Well-nourished women usually lose

supported by exclusive breastfeeding even in warm,

0.5 to 1.0 kg per month, whereas undernourished

humid climates. In contrast, excess fluid intake could

mothers lose an average of only 0.1 kg per month.

negatively influence milk production. When water is

Assuming energy content of 27 200 kJ/kg, the rate of

restricted, urinary output decreases before there is any

weight loss in well-nourished women would corre—

reduction in milk volume. Adapting fluid intake to

spond to the mobilization of 27 200 × 0.8 kg/month =

thirst is probably the best advice for lactating mothers

21 800 kJ/month, or 720 kJ/day (170 kcal/day) from

(Table 7.3) [42].

body energy stores. This amount of energy accounts in

 deduction from the energy cost of lactation. Thus, dur-may show great variation depending on population ing the first 6 months of lactation, the energy require—

and diet, and the ARA:DHA ratio may change from

ment of a lactating woman represents around 2100

2.8 to 0.4. The ability to synthesize DHA from ALA

kJ/day (500 kcal/day). After 6 months, the contribu—

exists in humans, but most evidence indicates that it

tion of weight loss is minimal – 22 kJ/day – and

is limited. Therefore, adequate intake of preformed n-3

does not significantly influence the energy cost for

LCPUFA, and in particular DHA, appears to be impor-

milk production – 1900 kJ/day (460 kcal/day; Table

tant for maintaining optimal tissue functions. Several

7.3). However, undernourished women and those who

studies have shown visual and cognitive advantages in

did not gain adequate body weight during pregnancy

infants after maternal supplementation with oily fish

must conserve as much energy as possible for their

or oils providing n-3 LCPUFA during pregnancy and

own health, and the full energy demands of lacta—

lactation. Supplementation of lactating women with

tion must be provided by an increment in dietary

200 mg DHA per day increased human milk content

intake [9–11].

up to a level considered desirable for infant outcomes.

New recommendations have been published con—

However, intakes of up to 1 g per day of DHA or 2.7

cerning protein requirements during lactation because

g per day n-3 LCPUFA have been used in randomized

previous recommendations did not take into consid—

trials without significant adverse effects. Women can

eration the nonprotein nitrogen fraction of human

meet the recommended intakes of DHA by consum—
milk. A factorial approach was taken to derive the pro—
ing one or two portions of sea fish per week, including
tein requirements during lactation. Mean production
oily fish such as herring, mackerel, and salmon (Table
rates of milk of well-nourished women who breast-
7.3). Even if fish can contribute to the dietary expo-
feed exclusively during the first 6 months and par—
sure of contaminants, these recommendations rarely
tially breastfeed during the second 6 months postpar—
exceed the tolerable intake of environmental contam—
tum were used, together with the mean concentrations
inants. Levels of bioaccumulative contaminants tend
of protein and nonprotein nitrogen in human milk,
to be greater in large fish that are higher in the food
to calculate milk protein output. The protein require—
chain (i.e. marlin, pike, swordfish, and shark) [16, 18,
ments were calculated as mean + 1.96 standard devia-
24, 25].
tion. The additional safe protein intake during the first
Cholesterol is synthesized in part by the mammary

6 months of lactation is 19 g of protein per day, falling
gland, and its level in milk is not affected by mater—
to 12.5 g of protein per day after 6 months (Table 7.3).
nal diet. Industrially produced trans fatty acids are fre—
New estimates are 20% to 50% higher than previous
quent in modern diets, and their presence in human
ones [14, 23].
milk reflects mothers' dietary intake. The literature
Maternal dietary preferences and the nature of her
includes controversies about trans fatty acids because
dietary fat have a great impact on milk triglyceride
of their association with long-term adverse biological
composition. Fatty acids from maternal diet may affect
effects [43, 44].
up to approximately 30% of total milk fatty acids. High
Dietary food allergens can be detected in breast
carbohydrate intake is associated with an increase in
milk and may induce allergic reactions in infants who
endogenous synthesis of C6–C16 fatty acids. In case of
are known to be clinically allergic to the antigen. Rare
insufficient diet, mother fat depositions are mobilized,

cases of anaphylaxis to cow’s milk protein present

and milk fatty acids tend to mimic their fatty acid comin human milk have been described, even in exclu—

position. When excessive non-fat-caloric diet is pro—

sively breastfed infants. Previous American Academy

vided, milk-saturated fatty acids increase as lipids are

of Pediatrics publications have advised lactating moth—

synthesized for tissue stores. When corn oil is the mean

ers with infants at high risk of developing allergy to

fat source, milk levels of C18:2 and C18:3 are higher,

avoid peanuts and tree nuts and to consider eliminat—

with a major increase in LA, compared with lard or

ing eggs, cow’s milk, and fish from their diets while

butter fats. Synthesis of fatty acids up to 16 carbons,

nursing. According to more recent studies, their advice

as well as desaturations of stearic acid into oleic acid,

was recently revised to state that in infants at high risk can take place in the mammary gland, whereas LCPU—

of developing allergy, there is no convincing evidence

FAs come directly from plasma and are directly related

for a long-term preventive effect of maternal diet dur—

to maternal diet. DHA concentrations in human milk

ing lactation on atopic disease (Table 7.3) [34, 35, 45].

r Human milk fat content is the main source of

Maternal milk protein content is preserved when lac—

energy and its most variable constituent.

tating mothers receive short-term marginal dietary

r The quality of dietary lipid supply, especially

protein intake. During World War II and the Dutch

DHA, in early childhood is a major

famine, pregnant women developed some maternal

determinant of infant development and

stores in anticipation of lactation, even if their fetus

long-term health. LCPUFA in human milk is

had intrauterine growth restriction. This demonstrates

derived from blood plasma and so is

the mother’s body’s strong biological commitment to

dependent on maternal diet. Eating fish twice

preparing for lactation. When the diet is insufficient,

a week and/or 200 mg DHA supplementation

fat deposits are mobilized and milk fat mimics the per day increases human milk content to a composition of fat stores. Protein content in milk level considered desirable for infant outcomes. from poorly nourished mothers is still in the range of normal values, and malnutrition has little impact on protein concentration. Malnutrition may decrease

Conclusions

production and secretion of immunological system Exclusive breastfeeding is recommended during the components of human milk, but this remains contro— first 6 months after delivery and should be continued versial, and further investigation is necessary. It would after introduction of complementary feeding. There is be useful to consider whether the lactation perfor— remarkable similarity across populations with widely mance of women who do not meet their energy needs varying nutritional status when measuring human might be compromised, but testing this hypothesis milk volume and nutritional supplies, but there is also poses methodological challenges. Nevertheless, some

a wide range of individual variability. This is related to evidence suggests that in women with adequate fat

the adaptation of milk production to infant demand.

reserves, postpartum gradual weight loss up to 0.5

Maternal dietary stores, dietary preferences, and cul—

kg/week is not likely to have any adverse consequences

tural patterns should be considered in establishing recon lactation and nutritional supplies in term infants.

ommendations for lactating women. New recommen—

Nevertheless, dietary restriction to favor postpartum

dations have recently been published concerning both

weight loss should be discouraged (Table 7.3) [10,

infants' and lactating mothers' requirements, but these

42].

usually make minimal adjustments to account for a

woman's lifestyle. Women need to be well nourished

throughout gestation and to maintain adequate nutri-

Key clinical messages

tional intakes after delivery. Supplementing malnour—

r There is remarkable similarity in milk

ished mothers is advised to promote maternal as well

production throughout the world, independent

as infant health. Well-nourished lactating women have
of lifestyle and nutritional status. Production
a net increase in energy requirements to approximately
of adequate and abundant milk supply is
2100 kJ (500 kcal) per day, which can be met by a
usually possible even in inadequate diets.
small increase in a well-balanced diet. Restricted diets
r
and medications to lose weight are unwise, and mater—
Food supplementation during lactation in
nal stores will be used for lactation. There may be
areas with a high incidence of malnutrition
some variation in milk composition related to mater—
has generally little, if any, impact on milk
nal diet, especially concerning fatty acids. N-3 polyun—
volume. However, it improves maternal health
saturated fatty acids have decreased in Western diets,
and is always helpful.
with potentially adverse effects. A supplementation of
docosahexaenoic acid during lactation is advised.

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Section 2

Nutritional regulation and requirements for lactation and

Chapter

infant growth

8 **Changesinnutrientrequirementswith**

age after birth

Christopher H. Knight

Introduction

developed well in utero and those who have not;

may be different between the sexes; and may be

This chapter considers nutritional requirements of the

affected by environmental factors both directly

neonate during the period between birth and wean—

and indirectly (mother’s nutrition, for instance).

ing. Preterm babies are the focus of the next chapter, so for our purposes “birth” is full-term birth.

The truth lies somewhere between these two situations.

The World Health Organization (WHO)[1] recomFor many mother:young dyads, the good news pre-mends that exclusive breastfeeding be practiced until vails,

for others it is totally irrelevant because “breast”

6 months of age, and because the weaning process is

is replaced by “bottle.” This chapter focuses on breast—

normally a gradual one, I interpret birth to weaning

feeding. The baby probably has no more or less control

to mean the first half-year or so of life. This is a time

over the fulfilling of his or her requirements whether

of rapid growth, development, and maturation, partic—

breastfed or bottle-fed, but for the mother, the differ—

ularly of the nervous and skeletal systems. It is also a

ence is quite fundamental. She will feel that she has lit—

time of fat deposition. Appropriate nutrition is essen—

tle conscious control over either the amount or quality

tial if a healthy baby is to grow into a healthy toddler. In of her breast milk. For the most part, she must trust to

the developed world, the majority of full-term babies

nature to get it right, something that is rather difficult do exactly that, and attention is now focused on longer—

for inexperienced mothers to do without appropriate

term effects of early development, particularly asso—

support. In contrast, she has (or believes she has) excel—

ciations between early development and later obesity

lent control over the quantity of bottle milk and some
and metabolic disease. “Appropriate” nutrition encom—
control over its quality. Whether we consider exclu—
passes a range that lies between deficiency and excess,
sive breastfeeding, partial breastfeeding, or bottle—
and, where long-term health is concerned, excess may
feeding, there is one further piece of bad news:
be as damaging as deficiency. The scenario is totally
r Above all, requirements will differ according to
different in the developing world, where malnutrition
the “target” that is being set. In particular,
caused by dietary deficiency continues to be a major
maximizing instantaneous growth will not
threat to the life of the young child. WHO estimates
necessarily maximize long-term health but will
that 60% of deaths under age 5 years are attributable,
consciously or unconsciously be the target for
directly or indirectly, to malnutrition. This chapter
many babies and for many mothers.
focuses on the developed world.
To wean is to “accustom to the loss of its mother’s

Finally, it should be recognized that rigid adher—

milk” (Oxford English Dictionary), hence it is implicit

ence to the title would result in a rather short chap-

(strictly) that the requirements of the infants under

ter, because, for the most part, our understanding

discussion are met by breastfeeding, either exclusively

of “requirements” during early life equates to know—

or in part. Thus, there is good news and bad:

ing what average intake has been. Requirements comprise whatever is necessary to maintain normal healthy

r The good news: breast milk provides all the

body functions (maintenance), daily energy expendi—

nutrients a baby needs for healthy development in

ture above maintenance (primarily locomotion), and

the first 6 months of life [2].

growth. There is relatively little locomotion compo—

r The bad news: the baby’s requirements may be

nent in the neonate but considerable growth. Although

viewed differently by baby, mother, and health

growth is readily apparent, precise quantification

worker; may differ between babies who have

is difficult because it requires knowledge of body

 composition as well as weight, and definitive informa-still be to encourage catch-up growth to ensure normal tion on composition is lacking [3]. Dietary Reference neurological development [13].

Intakes data published by the U.S. National Academy

Although the “worst path” to long-term health can

of Sciences Institute of Medicine do not list any Esti—

be identified (Fig. 8.1), it is much less clear whether mated Average Requirements for the 0-to 6-month what we would currently regard as “healthy growth”

age group and give only one (protein) for 7 to 12

is necessarily the optimum weaning-age target (“best”

months [4]. Instead, Adequate Intakes data are pro-in Fig. 8.1). The recent reformulation of WHO Child vided, which are stated to be mean intakes. I use the Growth Standards represents best knowledge, but the

term “requirement” to mean best knowledge of what is

very fact that there was a need for revision demon—

needed for healthy growth. A number of recent reviews

strates the inherent difficulty. The old growth charts

of neonatal nutrition are available, and those wishing a

were largely based on information from formula-fed

more detailed account than that provided here are rec—

infants and are now believed to have seriously overes—

ommended to read Butte *et al.* [5].

timated optimal growth. It is unlikely that there will

be further need for revision in the foreseeable future,

and I show “best” and “healthy growth” as overlap—

ping (rather than identical) only to show that there are

Targets for requirements

some things we cannot know for certain. The inappro—

The “ideal” growth path is for a healthy baby to grow

priateness of the older growth charts has implications

into a healthy toddler and hence enjoy long-term

for the metabolic programming hypothesis. Much of

health (Fig. 8.1). Logical as this progression might the data on which the hypothesis is based will have seem, it is only recently that early growth has been

been obtained from formula-fed infants, fed (as we

shown to have long-term impact. This is the con—

would now consider) excessively. So it may be that

cept of metabolic programming, recently reviewed by

modest catch-up growth is appropriate for all small

Wells *et al.* [6]. Relationships between birth weight and babies (full-term and preterm).

risk of obesity, metabolic disease, and coronary heart

In addition to inappropriate birth weight and

disease have been demonstrated but are not always

absence of breastfeeding, another factor that will

straightforward. For instance, two cohorts of intrauter—

cause deviation from the optimum path is disease, of

ine growth-restricted babies born during the Second

the neonate, the breastfeeding mother, or both (Fig.

World War (Dutch famine and Leningrad-siege) have

8.1). Surprisingly little is known about the effects of

shown different adult outcomes, while adult obesity

infection on energy requirements of babies. In review—

may be associated with both low and high birth weight.

ing the field, Garza [14] concluded that resting energy It is body composition, and particularly the extent of expenditure “remains stable, increases minimally or is

internal fat depots, that are most likely to influence

raised up to 30% above baseline” during acute illness.

long-term health, and body weight is not a particularly

Historical estimates of a 13% increase for every degree

good measure of body composition. However, it is also

Celsius of fever were supported by some observations

now apparent that fetal growth is only part of the pic—

but not others. Clearly, there is a problem. Because dis—

ture. Metabolic programming takes place during both

ease cannot be predicted in advance, measurements

fetal and neonatal life [7], and it appears that low birth have been made during the illness and compared with weight combined with early catch-up growth gives rise

later, presumed “normal” determinations. If disease

to the worst possible outcome (Fig. 8.1) [8]. There can is followed by catch-up growth, the assumption is be little doubt which population is at greatest risk from

invalid, because energy expenditure will be increased

this combination. Cigarette smoking is the major cause

by the extra growth. The usual advice offered to breast—

of low birth weight [9], smokers are less likely to breastfeeding mothers is to continue breastfeeding, offering feed [10], and formula-fed babies have a higher growth additional or prolonged feeds if the baby desires. As rate and are more likely to become obese [11]. In set-discussed later in the chapter, any additional energy ting targets, there is always a need to balance short—

requirement is almost certain to be met. WHO advice

and long-term objectives [12]. Thus, although a rec-for babies suffering diarrhea and dehydration is to offer ommendation to avoid catch-up growth may be appro—

additional fluid while continuing to breastfeed. The

priate for full-term, healthy but small babies, for pre—

health benefits of breastfeeding are many and varied

mature babies, the recommendation would normally

[15] and are covered in a later chapter.

Section 2: Nutritional regulation and requirements for lactation and infant growth Healthy Healthy

Healthy

SGA

baby

LGA

mother

baby

Overfeeding

Disease

Disease

Disease

Healthy

“Best”

Overweight

growth

Weaning

Healthy

growth

Long-term

health

Healthy

baby

Weaning

Earlier

“check”

weaning

Breastfeeding

Healthy

“check”

growth

Long-term

health

Figure 8.1 Schematic of optimal (green) and suboptimal (red) growth paths. Top left: The optimal path comprises healthy baby, healthy growth (to weaning), and long-term health. Only one of many possible suboptimal paths is shown, in which the small-for-gestational-age baby exhibits catch-up growth to become an overweight weanling. That toddler has a reduced chance of achieving long-term health. Top **74**

right: The neonate’s requirements will increase with age and will probably be higher immediately after disease. Both the volume and the composition of breast milk can vary to meet those requirements. Maternal disease (mastitis, for instance) is likely to affect both volume and composition. Bottom left: There is debate over the optimum length of exclusive breastfeeding. Earlier weaning could result in a growth check, but equally breastfeeding could become

inadequate and also restrict growth.

Chapter 8: Changes in nutrient requirements with age after birth A number of studies have shown that some 20%

Meeting energy requirements: the

of breastfeeding mothers will suffer mastitis [16]. The **6-month debate** usual recommendation is to continue breastfeeding

and to pay particular attention to breast emptying if

Energy is essential to life, and hence, if immediate

possible, although in some studies (but not all), mas—

energy requirements are not met in some way, other

titis led to discontinuation of breastfeeding in a sig—

requirements become irrelevant. Because energy sup—

nificant proportion of mothers. There is little pub—

ply is variable in the natural world, mechanisms for

lished information on changes in breast-milk volume

depositing energy as fat and subsequently mobiliz—

or composition during mastitis, but by analogy with

ing it during times of need have evolved. Lactation

dairy species, it is likely that both will be altered

is a related mechanism, whereby energetic variation

(Fig. 8.1). Volume will decrease, but effects on comis significantly diluted by the mother. Because milk position will vary depending on the pathogen and

has evolved as a balanced food designed to meet the

severity of infection. In the absence of evidence to the

nutritional requirements of the neonate, it has been

contrary, it is probably safe to assume that the baby's

argued that an amount of milk sufficient to meet

requirements can still be met by exclusive breast—

energy requirements will automatically fulfill all other

feeding during mastitis, although it is not known what

requirements as well [17]. It is now recommended proportion of affected mothers will start to offer com-that exclusive breastfeeding be done for the first 6

plementary foods.

months of life [1], whereas previously the recommen-The final panel of Figure 8.1 introduces the issue dation was 4 to 6 months. The advice is a global one, of when to wean. There has always been consider—

more designed to correct malnutrition in the devel—

able variation in weaning practice, both within cul—

oping world than to dictate to Western mothers. It

tures across time and between cultures at the one time

also reflects the realization that earlier energy recom-

[12]. For babies in developing countries where hygiene mendations were considerable overestimates, based is poor and the energy and protein content of supple—

as they were on intake of poorly designed milk for—

mentary foods is less than ideal, weaning represents

mula and the new knowledge that early overweight

risk. Growth faltering is commonplace. In developed

could have deleterious effects in the long term. The

countries, the great majority of babies wean success—

change has been controversial [18] and has prompted fully with no impediment to their growth and do so examination of energetic sufficiency at 6 months. In

irrespective of exactly when or how it occurs. Never—

summary:

theless, in recent years, a debate has opened up regarding one particular aspect of exclusive breastfeeding

r

and weaning: the 6-month debate.

Additional energy requirements for growth in the

first few months of life mean that energy required

per kilogram of body weight decreases between

r Inappropriate fetal and neonatal growth can have

birth and 6 months [17].

a negative long-term impact.

r Because body weight increases, total energy

r The combination of small birth weight and rapid

requirement increases from around 1900 kJ/day at

catch-up growth may be particularly bad.

1 month to around 2600 kJ/day at 6 months and is

r Mothers should be strongly advised not to smoke

higher in boys than girls [19].

in pregnancy and to breastfeed rather than

r Energy balance calculations indicate a small

bottle-feed.

deficit in exclusively breastfed babies at 6

r Small-for-gestational-age babies should be

months, suggesting that complementary feeding

monitored particularly carefully to ensure healthy

may be necessary [20].

growth while avoiding excessive catch-up growth.

r However, the same data also indicate a small

r Mothers should normally be encouraged to

deficit at 4 months, and the analysis excluded data

continue breastfeeding during short-term illness

continuing beyond 6 months, so there may be a

of the baby.

bias against mothers committed to prolonged

r Similarly, mothers who develop mastitis should

exclusive breastfeeding.

normally be encouraged to continue

r Energy balance would be achieved with an intake

breastfeeding.

at 6 months of around 1 kg/day.

Section 2: Nutritional regulation and requirements for lactation and infant growth r Typical human milk yield data are around exclusive breastfeeding provides for all the protein

700–900 g/day, but mothers suckling twins can

requirements of the growing baby up to weaning. As

produce twice this amount [21].

for energy, protein is provided in balance with need

r Milk yield is positively related to suckling

rather than in excess; at a typical protein content

frequency and efficiency [22]; mothers of twins of 13 g/kg (mature human milk from standard U.K.

feed 15 or more times per day.

food composition tables quoted in Emmett and Rogers

r Mothers are accustomed to feeding frequency

[28]), 800 g/day of breast milk provides 10.4 g pro—

decreasing after the first few weeks.

tein against a calculated requirement of 9.95 g (calcu—

r Older babies do not always have the patience to

lated from Dewey *et al.* [27] and revised WHO infant empty the breast effectively at a feed.

growth curves). Requirements for all individual amino

r Increased feeding demand is often evident at

acids can also be met by exclusive breastfeeding, by

approximately 3 months and again at

either direct supply or metabolic interconversion [26].

approximately 6 months [3].

Relative to cow's milk, human milk contains signifi—

r Social factors such as length of maternity leave

cant amounts of nonprotein nitrogen, which may con—

will have a strong influence on the mother:young

tribute to provision of nonessential amino acids but

dyad at approximately 6 months.

probably has no other specific dietary function. Milk

r The limited data available indicate only small

protein content can fall if the maternal diet is defi—

differences in health status of babies breastfed for

cient in protein and be restored by supplementation

4 or 6 months [18].

[29], but there is little evidence to indicate any problem of milk protein content in developed countries Taking these various pieces of information into

[28]. Vegans have normal protein content in their account, I would conclude: milk [29].

r

r

Energy requirements can be met up to 6 months

Exclusive breastfeeding to 6 months meets all of

but require a significant level of commitment

the protein requirements of the healthy baby.

from both mother and baby, which may not

always be possible.

Meeting requirements for fat and

r Mothers wishing to exclusively breastfeed to 6

fatty acids

months may be encouraged to do so and advised

Milk fat provides more than half of the neonate's

of the likely need for increased feeding frequency.

dietary energy, but because energy provision has been

The Web site of the Australian Breastfeeding

discussed separately, this section considers the role

Association

that individual fatty acids play in growth and devel-

(http://www.breastfeeding.asn.au/index.html)

opment. In particular, the long-chain polyunsaturated

provides appropriate advice.

r

fatty acids arachidonic acid (AA) and docosahex—

Mothers wishing to start weaning before 6 months

aenoic acid (DHA) may have a special role to play in

may be encouraged to do so and provided with

brain and retinal development [31] and are present in appropriate advice regarding weaning foods.

breast milk at low levels that are strongly influenced

For a detailed account of neonatal energy require—

by maternal diet [32]. Omega-3 fatty acids (of which ments in the preterm infant, the reader is recom-DHA is one) have attracted a great deal of publicity mended to read Hulzebos and Sauer [24].

for their healthful properties, which has extended to

media interest in breast-milk DHA. Cow's milk does

not contain either DHA or AA, but it is added to some

Meeting protein requirements

milk formulas. The evidence for doing so is somewhat

Human milk contains considerably less protein than

circumstantial at present, although it is unlikely that

cow's milk and less than almost any other species [25].

there is any detrimental effect. Healthy term babies can

However, "Dietary protein requirements are at their

synthesize both DHA and AA from their respective

highest between birth and weaning to support high

precursors ␣-linolenic acid (LNA) and linoleic acid

rates of tissue formation" [26]. These apparently con-

(LA) provided they are present in the usual proportion

tradictory statements are nothing of the sort; Dupont,

of approximately 1.5% LNA and15% LA (an abnormal

drawing on an earlier review [27], made clear that excess of either precursor would inhibit the formation of the opposite product). There is a concern that LA or her fluid requirement, which is above the generally

has been increasing in the human diet and in breast

accepted breast-milk production level but well within

milk as dietary patterns have changed, but there is lit—

the physiological range (discussed earlier). Studies of

tle evidence to suggest that DHA availability has been

fluid requirements in tropical regions have indicated

compromised. Vegan and vegetarian diets contain little

no need for any fluid other than breast milk to 6

or no DHA but do contain LNA and LA in the correct

months and beyond [37], an important consideration proportions [33]. In addition to the possibility of detri-when water supplies may be contaminated.

mental effects on brain development, high levels of n-6

r Water supplementation is not necessary before

polyunsaturated fatty acids such as AA and LA have

weaning and should be discouraged.

been implicated as possible factors in inflammatory

bowel disease (IBD) [34]. Once again, the evidence is **Meeting requirements for** somewhat circumstantial.

r

micronutrients

The total fat content of breast milk is appropriate

as an energy source.

Consider the following:

r The fatty acid profile of breast milk is influenced

“A plentiful supply of breast milk from a mother

by maternal diet and may have effects on brain

eating an adequate diet should provide all the infant’s

development and IBD, but neither effect is proven.

requirements of vitamins, minerals and trace eler Breastfeeding mothers who express concern

ments” [28].

should be reassured and may be advised to

“All breastfed infants should receive 1.0mg of vita—

increase modestly their consumption of

min K oxide i.m. after the first feed is completed and

omega-3 oils.

within 6h of life. . . . All breastfed infants should receive 200 IU of oral vitamin D drops beginning during the

Meeting requirements for

first two months of life” [38].

The apparent contrariness can be resolved by an

carbohydrate

understanding of the rationale for vitamin K and D

Lactose is the principal carbohydrate in breast milk

supplementations. Vitamin K is required for produc—

and makes a significant contribution to energy sup—

tion of clotting factors and is present in breast milk

ply. Through provision of glucose, it is essential for

only at low concentrations. There is a proven associ—

brain and nervous tissue function. Consumption of

ation between breastfeeding and late-onset hemor—

800 g/day of breast milk with a lactose content of

rhagic disease, sometimes called VKDB (vitamin K

72 g/kg provides approximately 60 g of carbohydrate,

deficiency bleeding) [39], hence there is good reason from which the “adequate intake” figure is derived [4].

for supplementation. In contrast to the clear advice

Apart from its energetic role, lactose also enhances cal—

offered by the American Association of Pediatricians

cium and magnesium absorption [35]. However, its [38] there is no national U.K. policy, but most neona-principal function is energy provision, as discussed tal units offer vitamin K as a matter of routine. Vita—

earlier.

min D is the one micronutrient that does not have to

r

be supplied in the diet, because it is naturally synthe—

Lactose is the principal energy component of

sized in skin tissue by the action of sunlight (specif—

breast milk and is essential for provision of

ically ultraviolet B radiation). Deficiency causes the

glucose and hence nervous system function.

r

clinical condition of rickets in infants. Infant formula

Exclusive breastfeeding to 6 months meets

is supplemented and typically provides approximately

requirements for carbohydrate.

10 g/l, the recommended adequate intake being

5 g/day [4]. Breast milk provides less than one tenth **Meeting requirements for fluids** of this amount. Advisory bodies are reluctant to rec—

Fluid (water) requirements are stated to increase from

ommend that babies be exposed to sunlight, for fear

approximately 100 ml*kg*day at birth to approximately of the risk of increasing skin cancer incidence, hence

150 ml*kg*day at 6 months [36]. It is not clear whether the U.S. recommendation to supplement the breast-this is simply breast-milk intake or an actual calculated fed baby and the U.K. recommendation to supplement

requirement. If accurate, a 6-month-old baby weighing

the breastfeeding mother (10 g/day during preg-

8 kg would require 1200 ml of breast milk to achieve his

nancy and lactation) [40]. Breast-milk levels respond **Section 2: Nutritional regulation and requirements for lactation and infant growth** to maternal supplementation but not always in an r Current recommendations concerning vitamins K

entirely consistent fashion. Detailed information on

and D supplementation are appropriate.

variation in breast-milk levels of micronutrients can be

r Certain ethnic populations are at particular risk

found in Emmett and Rogers [28]. As suggested ear-for vitamin D deficiency.

lier, deficiencies of vitamins and minerals are rare in

r Appropriate maternal calcium intake will ensure

full-term breastfed babies in developed countries, but

adequate supply in breast milk.

one needs to be aware of ethnic differences. Vitamin

r Iron status of exclusively breastfed babies may

D synthesis requires greater light exposure in dark—

become marginal before 6 months, especially in

skinned races, for instance, and there is evidence of

small-for-gestational-age and/or rapidly growing

higher incidence of rickets among Asian communi—

babies.

ties in the United Kingdom (not necessarily related to

breastfeeding).

Calcium and iron deserve particular mention.

Requirements beyond 6 months of age

Calcium, together with phosphorus, is essential for

“ . . . you may want to wean later – into your baby’s second year, or healthy skeletal development [41], as well as for nor-later.”

mal cell functioning in most tissues. Skeletal growth is

rapid during fetal life and continues postpartum but

This quote is taken from the Australian Breast—

then slows. The aspects of neonatal calcium nutrition

feeding Association Web site. Different attitudes about

that currently receive attention are avoiding deficien—

breastfeeding are evident from comparing the wean—

cies (in developing countries) and optimizing intake

ing advice offered here (which relates almost exclu—

for long-term development, maximizing peak bone

sively to breastfeeding aspects) with that offered in

mass, and avoiding osteoporosis. Calcium levels in

the United Kingdom by the Food Standards Agency

breast milk are less than one third of cow’s milk lev-

(which hardly mentions it). Neither approach is wrong

els, and formula is intermediate, but the absorption of

or right, but the potential for confusion in the minds

calcium from breast milk is higher than that from for—

of mothers is evident. WHO advice, in contrast, is very

mula. The typical requirement of 200 to 250 mg/day

specific: “Practice exclusive breastfeeding from birth to

is fully met by average breast-milk intake from well—

6 months of age, and introduce complementary foods

nourished mothers [36] but may become marginal at six months of age (180 days) while continuing to in mothers on poor-quality diets or those who avoid

breastfeed” [44].

drinking milk [42]. Supplementation of the maternal It is not clear exactly what happens at 179 or 181

diet is recommended in such circumstances.

days. In developmental terms, there is nothing “mag—

Iron is the most abundant trace mineral in the

ical” about 6 months, although energy expended on

body, and its deficiency “is probably the most fre—

locomotion will presumably start to increase at about

quently observed nutrient deficiency worldwide” [43].

that time. Extension of the arguments detailed previ—

Requirements are met partly by dietary intake but

ously suggests that some mother:young dyads living

largely by internal turnover. Healthy, average-weight

in developed countries may be able to continue exclu—

babies that grow at average rates generally have iron

sive breastfeeding beyond 6 months and have require—

reserves that, taken together with intake from breast

ments met, but for the great majority the advice to

milk, are sufficient for the first 6 months of life, but low start weaning (introducing complementary feeds) at

birth weight compromises the initial reserve, and high

around 6 months would be sound and would recognize

growth rate depletes the reserve earlier, hence sup—

the tremendous individual variation in preferences of

plementation may be necessary before weaning. Butte

mother and baby. The Australian advice quoted almost

et al. [5] cited a number of references indicating nor-certainly does not mean to imply that exclusive breast-mal iron status of exclusively breastfed babies for the feeding can readily continue to a year or beyond,

first 6 months of life, but others recommend supple—

although that would be one interpretation. Unfortu—

mentation after approximately 3 months [36]. Breast-nately, the term “to wean” is often used inaccurately to milk iron content is largely unaffected by maternal iron

refer to either one of two specific events (the first com—

status. The more usual time for iron deficiency to man—

plementary feed or the last breastfeed) when it prop—

ifest is during weaning between 6 and 12 months of

erly refers to a lengthy and gradual process. Ortho-

age, particularly if cow’s milk is given [43].

dox Jewish women breastfeed for 2 years or more,

Chapter 8: Changes in nutrient requirements with age after birth following ancient guidance given in the Talmud [45],

of exclusively breastfed infants, perhaps because of

but that advice certainly does not mention exclusive

the less precise definition. Nonexclusive breastfeeding

breastfeeding. There has been little scientific study of

beyond 6 months is relatively common, but any deci—

exclusive breastfeeding beyond 6 months apart from

sion to continue breastfeeding for very prolonged

an elegant series of studies undertaken at the Univer—

periods (beyond 1 year) may be made for reasons of

sity of Helsinki in the 1980s [46]. Infants exclusively nurture rather than nutrition – that is, it feels good breastfed to 9 months had slower growth (length,

for mother, baby, or both. However, in a study of long—

not weight), poorer iron status (but no clinical ane—

term (12–43 months) partial breastfeeding, analysis

mia), and, as recently reported, increased atopic der—

of the rest of the diet concluded that breast milk was

matitis at age 20. Significantly, of 200 mother:young

supplying as much as 20% to 25% of the energy intake

dyads recruited to this last experiment, 36 were still

[48], assuming that intake was at or around its recom-exclusively breastfeeding at 9 months and only 7 at mended daily allowance.

12 months. These mothers were all committed individuals (only two were lost from the experiment) and

Summary

a rigid, baby-oriented protocol was applied to deter—

I shall leave the final word to the European Society for

mine at what point exclusive breastfeeding should

Paediatric Gastroenterology, Hepatology and Nutri—

stop (donated human milk was offered after a breast—

tion's Committee on Nutrition, which recently pub—

feed, and only when it had been needed twice were

lished a commentary paper [49] and concluded (with complementary feeds offered). In other words, exclu-great clarity): sive breastfeeding to 12 months is not easy. The same

r "Exclusive breastfeeding ...for about six months

conclusion can be drawn from the PROBIT (Promo—

is a desirable goal."

tion of Breastfeeding Intervention Trial) intervention

r "Complementary feeding ...should not be

trial, a large, multicenter study in Belarus designed

introduced before 17 weeks and not later than 26

to promote breastfeeding to WHO standards. Those

weeks.”

still exclusively breastfeeding at and beyond 6 months

numbered 251, or just 1.4% of the 17 046 recruited

From the available knowledge of neonatal require—

mother:young dyads [47]. In contrast to the Helsinki ments, I can find no basis for disagreeing with either study, this trial did not find any reduction in growth

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Section 2

Nutritional regulation and requirements for lactation and

Chapter

infant growth

9 **Comparisonbetweenpretermand term infants**

Mary Fewtrell and Sirinuch Chomtho

An infant born before 37 weeks of completed preg-nutritional practice. Such studies are most advanced in nancy is by definition preterm. With modern neona-preterm infants.

tal intensive care, survival is possible after as little This chapter covers the following topics:

as 23 weeks gestation. These infants present a major challenge in nutritional management because they are 1. the important differences in nutrient

born during a period of extremely rapid fetal growth: requirements in preterm infants compared with

the fetus normally trebles in weight between 24 and those in infants born at term and

36 weeks gestation, gaining 15–20 g/kg/day. The nutri-2. the practicalities of meeting these requirements tional requirements of preterm infants therefore dif-during the early postpartum period and following fer in many ways from those of healthy infants born at discharge.

term. The magnitude of this difference depends on a number of factors including

the degree of prematurity, events in utero that may have compromised fetal nutri- The discussion focuses on nutrition in relation to tion, the severity of illness during the neonatal period, the short-and longer-term health and development and its treatment.

of preterm infants. It does not attempt to provide a Fetal nutrient accretion does not occur at a uni-comprehensive review of nutrient requirements for form rate, and prematurity poses the greatest prob-preterm infants. For further information on specific lems for nutrients for which accretion occurs predom-nutrients the reader is referred to the recent review by inantly during the third trimester. For example, 90%

Tsang *et al.* [1].

of the bone-forming minerals calcium and phosphorus are acquired during the last 12 weeks, whereas body fat content increases from 1% of body weight at 20 weeks **Major differences in nutritional** gestation to 15% at term. Low reserves, combined with **requirements between preterm and** immature metabolic responses, have important consequences for the ability of preterm infants to adapt to **term infants**

postnatal life and withstand starvation.

Several approaches have been used to estimate the Previously, the main focus in feeding preterm

nutritional requirements of preterm infants, including infants was on meeting their nutritional needs, (1) measuring the composition of “reference fetuses”

preventing nutritional deficiencies, and promoting at different stages of gestation to estimate fetal accre-growth. However, evidence that early nutrition has tion rates for various nutrients, (2) nutritional balance biological effects on the individual with important studies in preterm infants, (3) relating nutrient intake implications for health has led to a conceptual to short-term growth, and (4) relating early nutrient change. Nutritional practice was previously under-intake to functional outcomes, both short term (e.g.

pinned largely by observational or physiological stud-infection, necrotizing enterocolitis [NEC]) and longer ies, or by small clinical trials designed to test for term. With increasing evidence that early diet has the effects of specific products

on nutritional status, long-term consequences (as discussed subsequently), growth, and tolerance. However, larger randomized there is greater recognition of the need for feeding rec-trials with short-and longer-term efficacy and safety ommendations to be based, where possible, on health testing have started to produce an evidence base for outcomes.

Chapter 9: Comparison between preterm and term infants infants frequently demonstrate growth faltering dur-Protein ing the neonatal period. Typically, a nutrient deficit Results from a number of studies show that protein accumulates during the early postnatal period when gain increases linearly with intakes between approx-the infant is sick, and there is a delay in establish-imately 2 and 4 g/kg/24 hours [2]. Thus, to achieve ing enteral feeding. However, many infants fail to nitrogen accretion at the same rate as seen in utero show catch-up growth and in the smallest, sickest during the third trimester, the preterm infant requires infants, in whom fluid restriction may be imposed substantially greater intakes of protein than would be for medical reasons, the deficit often increases pro- obtained by a term infant fed on breast milk providing gressively. A recent study of nutrient intakes in hospi-1 to 2 g/kg/day.

talized preterm infants found cumulative energy and There is evidence that both short-and long-term protein deficits of 406 kcal/kg and 14 g/kg at 1 week outcomes are improved by meeting the increased pro-and 813 kcal/kg and 23 g/kg at 6 weeks of age in tein requirements of preterm infants. A recent sys- infants less than 31 weeks gestation [8]. Recognizing tematic review [3] identified five randomized clinical this problem, recent guidelines have proposed higher trials (RCTs) comparing different protein intakes in enteral protein intakes of 3.8–4.4 g/kg/day in ELBW

preterm infants and reported improved weight gain (Ↄ 1 kg) infants, with a protein:energy ratio of 2.5

and higher nitrogen accretion in infants receiving for-to 3.4 g/100 kcal, and 3.4 to 4.2 g/kg/day in very mulas with higher protein content (≥ 3 g/kg/day but low birth weight (VLBW; Ↄ 1.5 kg) infants, with a Ↄ 4 g/kg/day). None of the studies examined cognitive protein:energy ratio of 2.6 to 3.8 during the “stable outcome. However, a study in 495 extremely low birth growing” phase [9], to prevent growth faltering and weight infants (ELBW)[4] suggested that in-

hospital to facilitate catch-up growth. It is important to mon-growth velocity had a significant impact on neurode-itor the actual protein intake received by the infant, velopment and growth outcomes at 18 to 22 months not just the prescribed intake, because fluid restriction postterm. Furthermore, preterm infants randomized and perceived feed intolerance often lead to a marked to receive a formula containing 2 g/100 ml protein difference between the two. Nutritional restriction showed better short-term growth than those fed a stan-for medical reasons must in all cases be weighed dard formula containing 1.45 g/100 ml and also had against the long-term consequences of suboptimal significantly better neurodevelopment at 18 months nutrition.

and 7.5 to 8 years [5]. The beneficial effects were greater for boys than girls.

It is important to consider energy intake together Amino acids

with protein intake because, if energy intake is low, Certain amino acids may be particularly important high protein intakes cannot be utilized, and the infant's in preterm infants. For example, a randomized trial metabolic machinery is stressed. The ratio of energy to of taurine supplementation in formula-fed preterm protein also determines the relative proportions of fat infants [10] showed some evidence of more rapid and lean tissue, and the composition of tissue gained auditory maturation in the supplemented group at in preterm infants varies according to their diet. At the equivalent of term. More recently, Wharton *et al.*

present, it is not known whether it is preferable for [11] reported that preterm infants with the highest a preterm infant to have a weight gain with 15% fat plasma taurine concentrations during the neonatal as in the fetus or 40% fat as in the term infant. The period have higher Bayley mental development index consequences of the altered fat distribution reported at 18 months and higher scores on the Wechsler Intel-in preterm infants at term-equivalent compared with ligence Scale for Children—Revised arithmetic sub-that of term infants at birth are also unclear [6]. How-test at age 7. Plasma arginine concentrations have been ever, in a randomized trial in preterm infants, despite found to be inversely related to the severity of respira-major differences in growth rates between diet groups tory distress syndrome, and low concentrations have during the neonatal period, there were no differences been reported in infants who develop NEC. A random-in growth or body fatness [7] between groups at 8 to ized trial of arginine supplementation versus placebo 12 years.

in preterm infants found a significantly reduced inci-Despite recognition of the importance of an adedence of NEC in supplemented infants [12], although **83**

quate protein intake for growth and outcome, preterm a recent Cochrane review [13] reported that follow-up **Section 2: Nutritional regulation and requirements for lactation and infant growth** of infants from this trial showed no difference in neu-and prostaglandins and affecting the expression and rodevelopmental disability between groups.

activity of a number of genes involved in metabolism.

Rapid accumulation of LCPUFA, particularly docosa-Energy hexaenoic acid, in the brain occurs from the third trimester to 18 months postpartum. Human milk

Most measurements of energy expenditure have, for contains both precursor EFA and adequate LCPUFA practical reasons, been performed on stable, growing for structural lipid accretion. However, infant for-preterm infants. There are no definite data suggest-mulas traditionally contained only the parent EFA.

ing an increased energy requirement in sick infants, Whether the addition of LCPUFA to preterm for-and, in practice, the main challenge is ensuring that mulas results in improved clinical outcome remains the desired nutrient intake is actually received by the controversial and has been the subject of numerous infant in the face of fluid restriction due to the under-studies. One systematic review [16] concluded that lying illness and poor feed tolerance. Current recom-supplementation results in more rapid visual matu-mended intakes are 110 to 130 kcal/kg/day for healthy, ration that is transient, whereas a Cochrane system-growing preterm infants [14], assuming a target weight atic review [17] concluded that there was no convinc-gain of 16–20 g/kg/day.

ing evidence of cognitive benefit associated with supplementation. Two more recent studies reported some Fat

evidence for a beneficial effect of LCPUFA supplemen-Fat provides about half the energy for infants fed tation on neurodevelopment [18, 19], but no study has human milk. Preterm infants have lower fat absorption yet reported follow-up data beyond 2 years, and all than term infants, largely because of reduced intesti-studies in infants use tests of global cognitive function.

nal lipase activity. Although fat absorption from fresh LCPUFA supplementation

may result in more subtle breast milk may be as high as 90%, the range is large, effects on areas of development that may be detected and the figure is considerably lower from formula feeds only by using more specific tests at a later age. Fur-or from pasteurized human milk in which the lipases thermore, given the bioactive nature of LCPUFA, it have been denatured.

is plausible that supplementation may have long-term The type of fat is also important. Most modern for-effects on other outcomes, as suggested recently for mulas contain a fat blend designed to mimic the pat-body composition [20] or cardiovascular risk factors tern of fatty acid saturation and chain lengths found in [21].

breast milk. When compared with breast milk, these Another important consideration is whether the mixtures have a reduced content of fatty acids ester-addition of selected LCPUFA is safe. Various strategies ified to glycerol in the 2 position and an increase in have been used to supplement formula with LCPUFA, those esterified in the 1 and 3 positions. The latter and they have not been without problems. There is a undergo hydrolysis in the gut, releasing palmitic acid, fine balance between the relative amounts of linoleic which is poorly absorbed and tends to form calcium and linolenic acids and their longer-chain products, soaps. These soaps may be partly responsible for the and it seems probable that the inconsistent findings harder stools seen in formula-fed infants and occa-in randomized trials may relate more to the different sionally result in bowel obstruction, as well as influenc-strategies and doses used to supplement the formula ing calcium absorption. Studies using a modified fat rather than to the actual LCPUFA themselves [22].

blend (Betapol) containing a higher proportion of fatty These issues require further investigation.

acids esterified in the 2 position to mimic that found in human milk show increased calcium absorption and fat absorption in term and preterm infants [15].

Calcium and phosphorus

The role of n-3 and n-6 long-chain polyunsatu—

The calcium and phosphorous requirements of the rated fatty acids (LCPUFA) in preterm nutrition has preterm infant have received considerable attention, been extensively investigated in recent years. These because of the high incidence of

metabolic bone dis-LCPUFA are synthesized from precursor essential fatty ease (MBD) in this population. The majority of skele-acids (EFA) and found in high concentrations in the tal mineral is acquired during the last trimester, with central nervous system. In addition, LCPUFAs are intrauterine accretion rates of 140 and 75 mg/kg/day **84**

highly bioactive, acting as precursors for eicosanoids for calcium and phosphorus, respectively. Human milk **Chapter 9: Comparison between preterm and term infants** fed at 200 ml/kg/day provides at the most 60 and 30

substantial quantities of iron and do not need sup-mg/kg/day, making the in utero rate of skeletal min-plements until these are discontinued. A trial of high eralization impossible. Calcium absorption from the (20.7 mg/l) versus normal (13.4 mg/l) iron formulas in gut further limits accretion, being 50% to 70% from preterm infants found no difference in weight gain nor human milk and as low as 20% from formula milk.

development at 12 months postterm [26]. However, Phosphate absorption is better – approximately 90%

a recent trial in VLBW infants receiving early versus to 95% from both human milk and formula. How—

late (14 days vs. 61 days) enteral iron supplementation ever, when in short supply, it is used preferentially for showed a trend toward a beneficial effect of early sup-tissue synthesis rather than bone mineralization. It is plementation on long-term neurocognitive and psy-now recognized that the cause of MBD in preterm chomotor development at age 5 years [27].

infants is an inadequate supply of mineral, particularly phosphorus, rather than a deficiency of vitamin Zinc

D. Although MBD is usually asymptomatic, full-blown rickets and fractures may occur in severe cases.

Zinc plays a critical role in cell replication and growth Preterm infants fed human milk with its low min-and accumulates in the fetus during the last trimester eral content are at greatest risk of developing MBD

at around 250 g/kg/day. Dietary zinc together with unless they receive

phosphorous supplements. Those release of zinc from body stores usually provides an receiving modern preterm infant formulas should not adequate supply for the first few weeks of life, although require supplements. Current recommendations sug-zinc deficiency has been described as a late conse-gest an enteral mineral intake of between 120 and 200

quence of preterm birth (2–4 months). The amount of mg/kg/day of calcium and 70 and 120 mg/kg/day phos-zinc provided by 200 ml/kg/day of human milk falls phorus, with a calcium:phosphorus ratio of 1.7:2.0, from 1650 g on the first day of lactation to 160 g and a 25-OH vitamin D intake of 200 to 1000 IU/day after 4 months. Therefore, human milk collected dur-

[23]. Although many preterm infants weighing less ing the early (but not later) months of lactation theo-than 1.5 kg show evidence of reduced bone mineral-retically provides enough zinc to meet in utero accre-ization during the neonatal period, most are asympto-tion rates. A randomized study in preterm infants fed matic and appear to show catch-up in mineralization either a zinc-supplemented or placebo-supplemented during the first few years of life [24]. An important term formula from the time at which they reached 1.8

question is whether early MBD has any long-term kg for 6 months showed higher plasma zinc levels, sig-consequences. There is some evidence suggesting that nificantly greater linear growth velocity, and higher even silent early bone disease retards linear growth up motor development scores in the supplemented group to 10 years later [25]. However, follow-up of preterm [28]. The value of zinc supplementation for the long-infants into early adult life suggests that those who term development and growth of preterm infants is received unsupplemented human milk (with very low thus an area requiring further investigation.

early mineral intakes) have larger bones and a higher bone mass than those who received infant formulas Vitamins

(Fewtrell, unpublished). The significance of this find-Preterm infants may have special requirements for ing for bone health and osteoporosis risk in later life is some vitamins because of the following factors: uncertain.

1. They are born with low body stores, especially of the fat-soluble vitamins, which normally

Iron

accumulate during the third trimester.

Preterm infants normally have adequate iron stores for 2. They have reduced absorptive capacities for some the first 6 to 8 weeks of postnatal life, although they vitamins (e.g. vitamin E).

may be depleted more rapidly by frequent blood sam-3. They may benefit from “pharmacological” doses pling. Beyond this, an iron intake of 2 to 3 mg/kg/day of some vitamins. For example, meta-analysis of from all sources is recommended to prevent iron data [29] from six trials of intramuscular vitamin deficiency anemia, continuing until 12 months or A supplementation identified beneficial effects in until full mixed feeding provides an adequate iron terms of reducing death or oxygen requirement at **85**

intake. Infants receiving regular blood transfusions get 36 weeks gestation and 1 month of age and a trend **Section 2: Nutritional regulation and requirements for lactation and infant growth** toward reduced incidence of retinopathy of born preterm and randomized to human milk during prematurity. There is also some evidence from a the neonatal period had significantly lower blood meta-analysis of 26 RCTs that oral vitamin E

pressure and a more favorable lipid profile than those might reduce the incidence of severe retinopathy who received PTF, with a dose-response effect between and intraventricular hemorrhage. However,

these outcome measures and the proportion of human high-dose vitamin E (serum tocopherol Ċ 3.5

milk in the neonatal diet [33, 34]. The effect sizes mg/dl) was associated with an increased risk of observed in these studies were of a magnitude poten-sepsis [30].

tially important in public health terms in reducing the risk of cardiovascular disease. Interestingly, children **Achieving optimal nutrition in** who received human milk also had evidence of lower **preterm infants**

insulin resistance and better arterial distensibility (an early marker of vascular disease) than children from Despite greater appreciation of the importance of

ade-the PTF group (who had similar vascular function to quate nutrition for outcome in preterm infants and the children born at term) [35]. These effects appeared existence of specific nutritional recommendations, it is to be mediated by growth predominantly during

widely recognized that these infants often exhibit sub-the first 2 weeks of postnatal life and are consistent optimal growth, which may persist for some time after with the hypothesis that promoting growth early in hospital discharge and which may have adverse conse-the neonatal period may not be optimal for certain quences for cognitive outcome [4]. One practical prob-aspects of longer-term cardiovascular health [35].

lem for preterm infants following delivery is the initial Given these health benefits, it is important that inability to tolerate enteral feeds in sufficient amounts mothers are strongly encouraged to provide their own to ensure an adequate nutritional intake. In this situa-breast milk for their infant. However, because preterm tion, nutrition should be provided parenterally, start-infants are generally unable to breastfeed effectively ing with amino acid and dextrose solutions during before 34 weeks, the mother needs to express her milk the first day and rapidly building up to full nutri-

(sometimes for a prolonged period), which can then ent requirements, including lipids. Parenteral nutri-be fed to the infant through a nasogastric tube, cup, tion should not be stopped until full enteral feeds are or bottle. This process makes great demands on the convincingly tolerated. Minimal enteral feeding – the mother, and the importance of adequate support and practice of introducing small, nonnutritional quanti-advice cannot be overstated.

ties of milk to promote gut maturity – can proceed Despite the proven health benefits of human milk, alongside parenteral nutrition and results in a reducin nutritional terms it does not meet the needs tion in time taken to tolerate full enteral feeds and a of preterm infants for several nutrients, including shorter total hospital stay [31].

protein, energy, and minerals. To achieve adequate The following options are available for enteral feed-growth, avoid MBD, and, potentially, maximize cog-ing in preterm infants: nitive outcome, human milk can be fortified with r Human milk

a human milk fortifier (HMF), derived from cow's milk, which is mixed with the mother's own breast – Mother's own: "preterm milk" (MBM)

milk before it is given to the infant. HMFs have been – Banked donor milk (DBM)

shown to improve short-term weight gain, linear and – Fortified human milk

head growth, nitrogen retention, and blood urea levels r Preterm infant formula (PTF)

[36]. However, long-term benefits have not been estab-r Term infant formula (TF) lished, and the addition of an HMF may interfere with some of the anti-infective properties of human milk.

Human milk has significant advantages for

Although HMFs continue to evolve, the addition of preterm infants in both the short term (better feed a fixed amount of fortifier to breast milk of variable tolerance, reduced risk of infection and NEC) and the nutritional content means that the nutritional intake longer term. Preterm infants fed MBM have higher of the infant remains unknown, with the possibility developmental scores at 18 months and higher IQs at that the intake of some infants will remain subopti-7.5 to 8 years than those fed on other diets, even after mal, whereas in others, it could exceed the upper rec-86

adjusting for confounding factors [32]. Adolescents ommended limit for certain nutrients. A small RCT

Chapter 9: Comparison between preterm and term infants [37] showed that "adjustable" fortification of human cation or mineral supplements, often as the sole diet.

milk (based on the infant's blood urea concentra-It is not clear whether similar effects would be seen tion) resulted in greater weight and head circumfer-when DBM is used in a more "modern" context – as ence gains, which were significantly correlated with a supplement to MBM and supplemented with min —

protein intake, compared with "standard" fortification.

erals and/or HMF. Schanler *et al.* [41] performed an The development of a "humanized" milk fortifier, pro-RCT examining the use of fortified DBM or PTF as a duced from pooled DBM processed to ensure the high-supplement to MBM and was unable to establish any est safety standards, represents a potential advance short-term benefit for DBM over PTF. However, the because this would avoid exposure to cow's milk pro-study was only powered to detect a difference of 25%

tein. However, the issue of uncertain nutrient intake in the rate of NEC between DBM and PTF groups; a would remain. Clinical trials of this new fortifier are larger trial is required to address this issue specifically.

under way.

DBM is expensive and often in short supply. There is When MBM is unavailable or is insufficient to meet a generally accepted need for more research to estab-the infant's full enteral requirements, the options are lish whether DBM as used in modern neonatal units to supplement with DBM or PTF. DBM is derived

is beneficial and safe, to identify groups of infants who from unrelated women who are breastfeeding either benefit most, and to examine cost-benefit issues.

a preterm or term infant and who have "spare" milk.

Preterm infant formulas are designed specifically Donors are screened in the same way as blood donors, to meet the increased nutrient requirements of this and milk is pasteurized to remove the risk of trans-group. They promote more rapid growth [42], result in mitting infection. The process of collection, freez-earlier discharge, and reduce the incidence of hypona-ing, thawing, and heat treatment [38] can damage tremia and MBD when compared to unsupplemented antimicrobial factors in milk such as lysozyme, lacto-human milk. In addition, in a large RCT, infants ran-ferrin, immunoglobulins, and denatured milk lipase; domized to receive PTF during the neonatal period milk cells seldom survive the banking process. For had significantly better developmental scores at 18

this reason, it cannot be automatically assumed that months and 7.5 to 8 years than those randomized to the benefits shown for MBM will necessarily apply to a standard "term" formula [5, 43]. The advantages of DBM.

PTF over TF were greatest in small-for-gestational-age The milk of mothers who

have delivered preterm and male infants. However, PTF also has some disad-infants has a different composition from that of moth-vantages; in the short term, it is less well tolerated than ers delivered at term [39], with a higher concentra-human milk with an increase in vomiting, abdominal tion of total nitrogen, protein nitrogen, sodium, chlo-distention, and risk of NEC.

ride, magnesium and iron, and copper and zinc, and For many years, standard TFs were used as an alter-a raised immunoglobulin A content in early lactation.

native to human milk for preterm infants. However, The differences may relate to the low volume often pro-they contain inadequate nutrients to meet the require-duced by preterm donors. This milk is thus more suit-ments of the preterm infant. These formulas have litable than term donor milk for feeding preterm infants, tle place in the nutritional management of preterm particularly in view of its higher concentration of pro-infants below 2 kg in body weight.

tein. However, protein intakes from preterm human milk are variable and, by the second month, often fall to values at which theoretical needs would be met only Postdischarge nutrition in preterm infants

at very high volume intakes.

The nutrition of preterm infants after they leave the A recent systematic review [40] that compared out-neonatal unit has historically been relatively neglected.

come in preterm infants fed DBM or formula iden-At this rather arbitrary time point, breast-milk fortified only seven studies, five of them RCTs. Meta-tifiers are stopped, or the infant is changed to a analysis of data from three trials suggested that infants TF designed to meet the nutrient requirements of a fed DBM had a significantly reduced risk of develop-healthy full-term infant, despite the fact that many ing NEC (risk ratio 0.2), although feeding DBM was infants are still preterm and growth retarded at the also associated with slower neonatal growth. However, time. Many infants born appropriate for gestational all of the studies considered were 20 to 30 years old age become growth retarded during their neona-

and from an era when DBM was fed without fortifi-tal course, and data suggest that these early deficits **Section 2: Nutritional regulation and requirements**

for lactation and infant growth persist to some degree into infancy and child- Breast-feeding postdischarge hood [24]. However, although children born preterm It is unclear whether unsupplemented breast milk remain, on average, shorter and lighter than children meets the nutritional requirements of preterm infants born at term, there is no evidence that nutrition dur-after discharge. Although the proportion of moth-ing the period of hospitalization has any long- term ers exclusively breastfeeding their infant after dis-effects on growth [44]. It is unclear whether nutri-charge is still relatively small, a greater proportion tion during the period after hospital discharge ("post-of infants receive some breast milk for the first few term") influences longer-term growth. The small size weeks after discharge. A number of studies, inevitably of preterm infants at discharge is likely to be associ-nonrandomized and generally small, reported slower ated with deficits of a variety of nutrients, including growth rates and lower bone mass in human milk-calcium and phosphorus, zinc, and iron. Such deficits fed infants in the short term. Lucas *et al.* [47] stud-will inevitably increase in infants fed TF or unsupple-ied 65 preterm infants who were breastfed for at least mented breast milk after discharge.

6 weeks after discharge. Although similar in size to Four dietary options are available for use in

formula-fed infants at discharge, by 6 weeks postterm, preterm infants after hospital discharge:

breastfed infants were significantly lighter and shorter r human milk,

than formula-fed infants (on average 513 g lighter r term infant formula,

and 1.6 cm shorter than infants fed PDF). Slower r preterm infant formula, and

growth persisted up to 9 months postterm, by which r

time all the breastfed infants were receiving TF and nutrient-enriched postdischarge formula (PDF).

solids, although there were no significant differences in head growth between diet groups. Collectively, these Lucas *et al.* [45] reported extremely high mean daily data suggest that preterm infants who are breast-milk intakes in preterm infants fed TF after discharge, fed after discharge grow more slowly and have lower reaching 230 ml/kg before 4 weeks postterm and bone mass in the short

term than formula-fed infants.

remaining over 150 ml/kg/day beyond 6 months. Thus, It is currently unclear whether this has longer-term given the opportunity, preterm infants will clearly con-consequences.

sume a significantly greater quantity of nutrients than would be provided by TF fed at 150 ml/kg/day as recommended for term infants. One solution is to con-

Introduction of solid foods

tinue the use of PTF beyond discharge. However, the-There are few data to guide either the optimal age for oretical concerns that infants fed on demand might introducing solid foods or the optimal type of solid consume high volumes of PTF with potentially toxic foods for preterm infants. The introduction of solids intakes of certain nutrients, such as vitamin D, led to is likely to result in a reduction in milk intake. If the the development of special PDFs. These contain (1) quality of solid food is poor, this may result in a reduc-higher protein content to promote catch-up growth, tion in overall nutrient density that could compromise accompanied by a modest increase in energy to allow growth and nutrient status. In a recent study, preterm utilization of the additional protein (a substantial infants were randomized either to “current” weaning increase in energy content might promote excess fat practice or to a “new solid food strategy,” which rec-deposition and lead to the infant’s downregulating for-ommended early weaning (from 13 weeks chronolog-mula intake), and (2) additional calcium, phospho-ical age) and the use of foods with a higher energy, rus, zinc, trace elements, and vitamins to support bone protein, iron, and zinc content. The intervention group mineralization and the projected increase in growth achieved increased protein and energy intake and bet-rates.

ter iron status by 6 months postterm and had improved Five RCTs reported increased weight and/or length linear growth velocity at 12 months [48].

in infants receiving PDF or PTF after discharge compared to TF [44]. However, a more recent study [46]

Early nutrition and later health in reported slower growth in infants fed PDF compared with those randomized to TF. There are currently no **preterm infants: an overview** follow-up data on growth and development in later Recent

evidence suggests that human milk has an **88**

childhood.

important place in neonatal intensive care. Human **Chapter 9: Comparison between preterm and term infants** milk is better tolerated than formula, and enteral feeds growth and bone mineralization seen in these infants.

can be established faster, reducing the requirement for In practice, it is difficult to envisage how nutritional parenteral nutrition with its known hazards. The use of supplementation could easily be given to a fully breast-breast milk is associated with a reduction in the inci-fed infant without interfering with the process of lac-dence of NEC and systemic infection and is associated tation. Nevertheless, because the majority of preterm with improved cognitive outcome, lower blood pres-breast-fed infants (particularly the smallest, who are sure, and more favorable plasma lipid profile during likely to be most at risk of growth problems) receive at childhood and adolescence. The slower initial growth least some formula milk, it would make sense for this rate seen in infants receiving human milk may be ben-to be PDF rather than TF. Another solution is to focus eficial for later insulin resistance and arterial distensi-more attention on the age of introduction of solid food, bility. However, in a preterm population, the risks and ensuring that the diet is of a high nutrient density.

benefits of promoting growth must be balanced; the adverse consequences of poor early growth for short-term survival and for later cognitive development out-Summary points weigh any slight increase in later cardiovascular risk r

associated with more rapid growth during very early Early nutrition affects both the short-term

postnatal life, and it is therefore essential to promote and longer-term health and development of

growth in these infants.

preterm infants.

r

We recommend the use of breast milk, preferably There are major differences in

the nutritional the mother’s own, but donor milk if it is not avail-needs of preterm infants compared with able, to establish enteral feeds. When mothers do not those of infants born at term, determined by

provide breast milk, PTF should be used. It may also the degree of prematurity, events in utero that be used as a supplement when mothers do not pro-may have compromised fetal nutrition, the duce enough breast milk to meet the infant’s require-severity of neonatal illness, and its treatment.

r

ments. Breast milk should be supplemented with phos-Early growth failure in preterm infants has phorus as a minimum, and a multinutrient fortifier adverse consequences for short-term

should be added if growth is unsatisfactory on the outcomes and for longer-term

maximum tolerated volume of breast milk. However, neurodevelopment and should be prevented.

preterm infants are not a homogeneous population, r Human milk has many health benefits for

and with the survival of ELBW babies, any single diet preterm infants including a lower risk of

is now unlikely to be optimal from birth to discharge.

infection and NEC, improved cognitive

Further work is required to explore how diets can be outcome, and reduced risk factors for

tailored to individual patients’ needs.

cardiovascular disease. However, in

After discharge (postterm), it is important to pro-nutritional terms it does not meet the vide adequate nutrition to facilitate catch-up growth requirements of preterm infants for several

and reverse nutrient deficits that accumulate postna-nutrients. It therefore requires tally. This can be achieved using a postdischarge for-supplementation with phosphorus as a mula. Available data suggest that preterm infants who minimum and generally with a

are breastfed after discharge might benefit from addi-multinutrient fortifier to ensure adequate tional nutrients, but longer-term outcome data are growth.

required to investigate the consequences of the slower

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Section 2

Nutritional regulation and requirements for lactation and

Chapter

infant growth

10**Influencesoftimingandddurationofformula feeding on infant growth**

William C. Heird

Introduction

To provide a historical perspective into the evolu-tion of modern infant formulas, this chapter begins All national and international groups responsible with a brief history of formula feeding. This is followed for making nutritional recommendations for infants by discussions of the types and composition of mod-endorse exclusive breastfeeding for the first several ern infant formulas available, the regulation of infant months of life [1–3]. Some state "for 6 months," oth-formula composition and marketing, the growth of ers state "for about 6 months," and still others state formula-fed versus breastfed infants, and the appro-

"for 4 to 6 months." Continued breastfeeding for as priate introduction of complementary foods for both long as 2 years or more along with timely introduction breastfed and formula-fed infants.

of appropriate complementary foods is also endorsed.

However, these bodies recognize that many infants, for a variety of reasons, either are not breastfed or are not breastfed for the recommended time. For these

History of infant formulas

infants, the only acceptable alternative is thought to be Despite attempts over several centuries to feed infants a modern infant formula. Thus, in the United States, who are not breastfed, modern infant formulas are where about 75% of infants are breastfed at hospital a relatively recent phenomenon. The patenting of a discharge but only about 30% are still breastfed at 4

method for condensing cow's milk by Borden in the months of age, at least 25% of all infants are fed for-late 1800s is usually cited as the major factor in mula (or another liquid) for the first year of life and development of modern infant formulas. However, 75% or more are fed formula (or another liquid) after other accomplishments were necessary before major 4 months of age. Breastfeeding is more common in progress was made. The introduction of glass bottles some other developed countries and particularly in and rubber nipples in the mid-to late 1800s made developing countries. Nonetheless, many infants are it easier to keep feeding utensils clean. In addition, formula-fed for a large part of the first year of life, and commercial-scale pasteurization was available by the those who are not breastfed or formula-fed receive a late 1800s, and sanitary, closed-top

metal containers variety of liquids that contribute to higher rates of mal-that allowed safe long-term storage of formula com-nutrition, morbidity, and mortality [4].

ponents and complete formulas were introduced in Although infants fed modern formulas do not

the early 1900s. Another crucial factor was knowledge experience many of the advantages afforded by human of the composition of human and animal milks and, milk (e.g. fewer common infections), they do quite hence, how to modify animal milks to more closely well. As stated by Fomon [5], "in industrialized coun-mimic the composition of human milk. Finally, by tries, any woman with the least inclination toward the early 1920s, the general level of sanitation had breastfeeding should be encouraged to do so and all improved and home refrigerators were available.

assistance possible should be provided by physicians, With more widespread use of formulas, it was real-nurses, nutritionists and other health workers. At the ized that scurvy and rickets were more common in same time there is little justification for attempts to formula-fed than in breastfed infants. These vitamin-coerce women to breastfeed. No woman in an indus-deficiency diseases were initially attributed directly to trialized country should be made to feel guilty because the use of the artificial formulas or failure to breast-she elects not to breastfeed her infant." As described feed, but eventually it was recognized that the prob-92

subsequently, this statement would not have been true lem was not formula per se but that the vitamins were as recently as about 60 years ago.

destroyed by heat processing.

Chapter 10: Influences of timing and duration of formula feeding on infant growth The advances in formula composition and manu-has been modified to include more lactose (unless facture between the late 1800s and early 1900s were intended for infants with lactose intolerance), and but-so dramatic that by the early 1900s, formula feeding ter fat has been largely replaced by mixtures of veg-was no longer considered hazardous, and pediatricians etable oils that are better absorbed than butter fat. As around the world began recommending a variety of described in the following section, all must support artificial feedings

for infants who could not be breast-normal growth for the first 4 to 6 months of life when fed. This, of course, led to the development and mar-fed as the sole source of nutrition.

keting of a number of complete formulas. One of these, Although the composition of infant formulas has a synthetic milk-adapted (SMA) product, was the fore-evolved over many years, research to improve accept-runner of a formula that is still available.

ability and nutritional quality continues. In general, Despite availability of complete formulas that human milk serves as a model for the composition of required only mixing with water before being fed to infant formulas, but it has been impossible to dupli-the infant, formulas made at home from evaporated cate the exact composition of human milk, which, in milk, sugar, and water remained popular until the late addition to nutrients, contains hormones, growth fac-1950s, by which time they had largely been replaced by tors, immunologically active agents, enzymes, cells, “complete” formulas. Initially, only powdered and con-and other factors [12]. In addition, the bioavailabil-centrated liquid products were available, but ready-to-ity of some nutrients in human milk is greater than in feed formulas were soon introduced. The convenience formula; thus, current efforts focus on duplicating the of ready-to-feed formulas made them quite popular, biological effects of human milk rather than its precise but recently, powdered formula has regained popular-content.

ity, probably because of its lower price and its conve-The most commonly used infant formulas are stannience for feeding away from home.

dard cow’s milk–based formulas, but for the past quar-Although some of the changes in formula com—

ter century, approximately 25% of all formulas sold in position and manufacture since the late 1960s are the United States have been soy-based. However, these important, changes during this time pale in compar-formulas are much less popular in most other coun-ison to previous advances. Perhaps the most impor-tries. A variety of hydrolyzed protein formulas with tant of the more recent changes is the availability peptides of different lengths are also available, as are and use of iron-fortified formulas, which are cred-formulas containing only amino acids. Each of these is ited with markedly reducing iron-deficiency anemia now discussed briefly.

throughout the world. In addition, a number of human milk components have been added to formulas over the past few decades [11]. These include taurine, Cow's milk–based formulas carnitine, nucleotides, and, more recently, the long- A standard cow's milk–based formula is the feeding of chain polyunsaturated fatty acids docosahexaenoic choice for normal term infants who are not breastfed acid (DHA) and arachidonic acid (AA). Currently, or are not breastfed for the recommended 12 months.

some formulas contain prebiotics and/or probiotics The nutrient composition of some of the most popu-that are thought to support the growth of benefi-lar cow's milk–based formulas is shown in Table 10.1.

cial bacteria and inhibit the growth of pathogenic The compositions do not differ appreciably. The pro-bacteria.

tein content of these formulas is either unmodified cow's milk protein or whey-predominant cow's milk protein, a mixture of cow's milk and demineralized **Composition of current infant formulas** whey proteins. The earliest such formulas had a ratio A number of formulas are now available for feeding of 60% whey proteins and 40% caseins, mimicking the normal term infant. There are also special for-the percentage of these two proteins in human milk.

mulas for feeding preterm infants as well as formulas Although it is now recognized that the composition for feeding infants with inborn errors of metabolism of human milk and bovine whey proteins and caseins (e.g. phenylketonuria) and diseases associated with differs considerably, such formulas remain popular.

gastrointestinal intolerance. Modern infant formulas More recently, formulas with other mixtures of caseins differ considerably from evaporated milk formulas.

and whey proteins (e.g. 48% whey proteins, 52%

They contain less protein, their carbohydrate content caseins) have become available. The plasma amino acid **Section 2: Nutritional regulation and requirements for lactation and infant growth** Table 10.1 Nutrient content (per liter) of representative cow's milk–based infant formulas **Enfamil R Lipil R** ∗

(Mead NAN R (Nestle, Glendale,

Similac R ∗ (Abbott, Johnson, Evansville, IN)

CA)

Columbus, OH)

Energy, kcal

680

676

676

Protein, g

14.5

15

14

Casein, % of total protein

40

40

52

Whey, % of total protein

60

60

48

Fat, g

36

35

36.5

Polyunsaturated, %

20

22

24

Monounsaturated, %

37

33

39

Saturated, %

43

45

37

Oils

Palm olein, high-oleic sunflower, soy,

Palm olein, soy, coconut,

High-oleic safflower, coconut,

coconut, DHA, AA

high-oleic sunflower, safflower,

soy, DHA, AA

DHA, AA

Carbohydrate, g

73

76

73

Lactose

Lactose, corn syrup

Lactose

Minerals

Calcium, mg

530

510

527

Phosphorus, mg

360

286

284

Magnesium, mg

54

48

41

Iron, mg

12.2

10.2

12.2

Zinc, mg

6.8

5.4

5.1

Manganese, g

100

48

34

Copper, g

510

544

608

Iodine, g

68

82

41

Sodium, mEq

8.0

7.1

7.1

Potassium, mEq

18.7

17.4

18.1

Chloride, mEq

12.1

12.5

12.4

Vitamins

A, IU

2000

2027

2027

D, IU

410

405

405

E, IU

13.5

13.6

10.1

K, g

54

54

54

Thiamine (B1), g

540

405

676

Riboflavin (B2), g

950

952

1014

Pyridoxine, g

410

510

405

B12, g

2.0

1.7

1.7

Niacin, mg

6.8

5.1

7.1

Folic acid, g

108

102

101

Pantothenic acid, mg

3.4

3.1

3.0

Biotin, g

20

14.9

29.7

Chapter 10: Influences of timing and duration of formula feeding on infant

growth patterns of infants fed formulas with modified and Soy-based formulas contain no lactose, making

unmodified cow's milk protein differ somewhat, but them appropriate for infants with lactose intolerance.

there is no convincing evidence that one mixture is Other indications include documented immunoglob-more or less efficacious than another [13].

ulin E–mediated allergy to cow's milk protein, doc-Fat provides 40% to 50% of the energy content of umented transient or congenital lactase deficiency, cow's milk–based formulas. This is usually a mixture of galactosemia, or simply the desire of the parents to vegetable oils, but some, primarily those intended for have their infant receive a vegetarian diet [16]. Soy-the European market, also contain a small amount of based formulas, like cow's milk–based formulas, can butterfat. As shown in Table 10.1, the fat blends of the also be used for infants whose nutritional needs are not common cow's milk–based formulas differ somewhat, met by human milk.

but all provide a mixture of saturated, monosaturated, The same vegetable oils used in cow's milk–based and unsaturated fatty acids, mimicking the balance of formulas are used in soy-based formulas. The mineral these fatty acids in human milk or the response of the and vitamin content of soy-based formulas, like the breastfed infant. More recently, small amounts of the content of protein, is higher than the contents of these long-chain polyunsaturated fatty acids DHA and AA nutrients in human milk or cow's milk–based formu-have been added to mimic the contents of these fatty las. This is thought to compensate for presumed lower acids in human milk [14]. The source of these fatty mineral availability, secondary, in part, to substances acids in most formulas is a mixture of single cell oils, in soybeans such as phytate.

but fish oils and egg yolk phospholipid are also available and are used in some formulas manufactured out-side the United States.

Protein hydrolysate formulas

There are some differences in fat absorption and These formulas were developed for infants who could mineral absorption as well as the plasma lipid profile not digest or were intolerant to both cow's milk and among infants fed the various combinations of oils.

soy protein. The protein is hydrolyzed to amino acids However, these are not marked. All current infant for-and peptides that are incapable of causing, or unlikely mulas are well tolerated, and all result in fat and min-to cause, an immunological response in most infants.

eral absorption that differ minimally from fat and min-Such formulas are indicated for infants who are intoleral absorption of breastfed infants.

erant of both cow's milk and soy protein and for those Although some cow's milk–based formulas contain with significant malabsorption secondary to gastroin-other sugars, lactose is the major carbohydrate of most, testinal or hepatobiliary disease. They also are used for and it is well tolerated by most infants. Some formulas infants with a strong family history of food sensitivi-also contain small amounts of starch or other complex ties, but it is not clear that use of these formulas prevent carbohydrates for technical reasons.

symptoms of food intolerances [17]. Although nutritionally efficacious, these formulas have an unpleasant taste, are expensive, and have a high osmolality.

Soy-based formulas

Formulas based on hydrolysates of cow's milk,

Modern soy-based formulas, like modern cow's milk– casein, and whey are available. The proteins are heat based formulas, support growth similar to that of treated and systematically hydrolyzed, resulting in a breastfed infants. The nutrient contents of some com-hydrolysate of free amino acids and peptides of varying mon soy-based formulas are shown in Table 10.2.

length. The hydrolysate is then supplemented with the Again, the compositions of the various formulas differ amino acids destroyed in the hydrolysis process. The minimally. Although native soy protein is deficient in available formulas contain different amounts of pep-methionine, the soy-based formulas are supplemented tides of varying chain lengths. More extensive hydrol-with methionine, which makes the nutritional qual-ysis results in less allergenicity but higher cost. Unfor-ity of this protein equal to that of cow's milk–based tunately, the allergenicity can be determined only by protein [15]. Nevertheless, soy-based formulas contain clinical trial.

about 25% more protein than cow's milk–based for-Most hydrolyzed formulas

are lactose free. They mulas, presumably because of the assumption that the may contain sucrose, corn syrup solids, tapioca starch, nutrient quality of soy protein (fortified with methio-corn starch, or other starches in various amounts.

95

nine) is less than that of human milk or cow’s milk.

Many hydrolysate formulas contain medium-chain Table 10.2 Nutrient content (per liter) of representative soy-based infant formulas **Prosobee R**

Good Start R Essentials

Isomil R

(Mead Johnson, Evansville, IN) Soy (Nestle, Glendale, CA)

(Abbott, Columbus, OH)

C (ascorbic acid), mg

81

61

61

Choline, mg

81

82

108

Inositol, mg

41

122

32

Energy, kcal

680

676

676

Protein, g

16.9

19

16.6

Source

Soy protein isolate

100% soy protein isolate

Soy protein isolate, L-methionine

Fat, g

36

34

37

Polyunsaturated, %

19

22

Monounsaturated %

38

33

Saturated, %

40

45

Oils

Palm olein, soy, coconut, high oleic

Palm olein, soy, coconut, high

High-oleic safflower, coconut, soy

sunflower

oleic safflower

Carbohydrate, g

72

74

69.6

Corn syrup solids

Corn maltodextrin, sucrose

Corn syrup solids, sucrose

Minerals

Calcium, mg

710

704

709

Phosphorus, mg

560

423

507

Magnesium, mg

74

74

50.7

Iron, mg

12.2

12.1

12.2

Zinc, mg

8.1

6

5.1

Manganese, g

169

228

169

Copper, g

510

805

507

Iodine, g

101

101

101

Sodium, mEq

10.4

10.2

12.9

Potassium, mEq

21

20

18.7

Chloride, mEq

15.2

13.5

11.8

Vitamins

A, IU

2000

2012

2027

D, IU

410

402

405

E, IU

13.5

20.1

10.1

K, g

54

54

74

Thiamine (B1), g

540

402

405

Riboflavin (B2), g

610

631

608

Pyridoxine, g

410

402

405

B12, g

2

2.1

3.0

Niacin, mg

6.8

8.72

9.1

Folic acid, g

108

107

101

Pantothenic acid, mg

3.4

3.2

5.1

Biotin, g

20

52

30.4

C (ascorbic acid), mg

81

107

61

Choline, mg

81

80

54

Inositol, mg

41

121

33.8

Chapter 10: Influences of timing and duration of formula feeding on infant

growth triglycerides to facilitate fat absorption, but they also regulations, with which the author is most familiar, are contain enough polyunsaturated vegetable oils to sup-discussed.

ply essential fatty acids.

The regulations provide specific controls for the nutrient composition, production, and marketing of Amino acid–based formulas

infant formulas. Current specifications for the nutrient composition of formulas marketed in the United States Formulas containing only amino acids are intended as well as other recent recommendations are shown in for use in infants with extreme protein hypersensitiv-

Table 10.3 [18, 21, 22]. Like the nutrient contents of ity, that is, those with persistent symptoms when fed available infant formulas, the recommendations of the an extensively hydrolyzed protein formula. These for-various groups differ minimally.

mulas are much more expensive than cow's milk– or The purpose of the infant formula provisions of soy-based formulas and are also more expensive than the regulatory acts is to protect the health of infants hydrolyzed formulas.

fed the infant formula product. These were strength-ened in the mid 1980s in response to a series of events Follow-up formulas

in the late 1970s. An infant formula manufacturer Follow-up, or follow-on, formulas are intended for in the United States changed its monitoring practices infants over 6 months of age. In general, they contain to exclude chloride, the concentration of which, his-more protein and more of some minerals than regu-torically, had been predictable from the sodium con-lar infant formulas. Part of the rationale for such a for-centration. However, the source of another ingredi-mula is to compensate for a possibly low protein intake ent was changed, negating the historical predictability and, particularly, a low iron intake after complemen-of chloride content from sodium content. As a result, tary feedings begin to displace human milk or formula chloride-deficient formulas were released, and infants intake. Although nutritionally adequate, these formu-fed these formulas developed chloride deficiency with las offer no advantage for infants whose diets contain hypochloremic metabolic alkalosis [23].

adequate iron and other nutrients from a combination This incident precipitated passage of the Infant For-of formula, complementary foods, and supplements.

mula Act of 1980, which amended the Food, Drug, Such formulas are popular in Europe and other parts and Cosmetic Act to ensure the adequacy of the nutri-of the world but are rarely used in the United States.

ent composition of infant formulas. Subsequently, the Moreover, advisory committees in Europe no longer statutory requirements for infant formula under the endorse use of these formulas [18], and they have never act were revised, giving the FDA even broader reg-been endorsed by U.S. advisory committees.

ulatory authority, including the requirements for the Whole and reduced-fat cow's milk is often used in nutrient content of infant formula, quality control pro-lieu of formula, in part because of its lower cost. Thus, cedures, record keeping, and procedures for "recall-availability of a simpler, less expensive formula for use ing" unsafe infant formula from the marketplace.

after 6 months of age would be a welcome addition.

Currently, infant formula manufacturers must

Availability of such a formula should delay introduc-submit information, including information on pro-tion of cow's milk, which has a high renal solute load cessing, to the FDA before any new formula or any for-and may contribute to fecal iron loss and anemia.

mula manufactured by a previously unknown manufacturer is marketed. The FDA has responsibility under the act to review the new infant formula submission **Regulation of infant formulas [19, 21]**

to enhance the likelihood that the product produced Infant formula is regulated as a food intended solely for will be safe. If the information in the submission meets infants, that is, it simulates human milk or is suitable as the requirements of the act, the FDA will not object a complete or partial substitute for human milk. In the to marketing of the formula. Interestingly, the FDA United States, marketing of infant formula is regulated is not authorized to "approve" infant formulas before by the federal Food, Drug, and Cosmetic Act and sub-they are marketed, but it has compliance authority if sequent regulations of the Food and Drug Adminis-an infant formula is marketed over its objections.

tration (FDA). Similar regulations are in place in most An infant formula submission must include a

other countries, but the details of these regulations dif-quantitative formulation and listing of all ingredients **97**

fer somewhat from country to country. Only the U.S.

in the formula, including amounts. Only ingredients Table 10.3 Recommendations for the nutrient content of infant formulas (amount/100 kcal unless otherwise noted) **FDA21**

LSRO22

ESPGHAN18

Minimum

Maximum

Minimum

Maximum

Minimum

Maximum

Energy (kcal/dl)

—

—

63

71

60

70

Total fat (g)

3.3

6.0

4.4

6.4

4.4

6.0

% energy

40

54

40

57.2

40

54

LA (% FA) **

2.7

—

8

35

75

27

ALA (% FA) ∗∗∗

—

—

1.75

4

2.5

—

LA/ALA

—

—

6 :1

16 :1

5 :1

15 :1

Protein (g)

1.8

4.5

1.7

3.4

1.8 (soy, 2.25)

3.0

Carbohydrates (g)

—

—

9.0

13

9.0

14

Carnitine (mg)

—

—

1.2

2.0

1.2

—

Taurine (mg)

—

—

0

12

0

12

Nucleotides (mg)

—

—

0

16

0

5

Choline (mg)

7.0

—

7

30

7.0

50

Inositol (mg)

4.0

—

4

40

4

40

Calcium (mg)

80

—

50

140

50

140

Phosphorus (mg)

30

—

20

70

25 (milk) 30 (soy)

90 (milk) 100 (soy)

Magnesium (mg)

6.0

—

4.0

17

5

15

Iron (mg)

0.15

3.0

0.2

1.65

0.3

2.0

Zinc (mg)

0.5

—

0.4

1

0.5

1.5

Manganese (g)

5.0

—

1.0

100

1

50

Copper (g)

60

—

60

160

35

80

Iodine (g)

5.0

—

8

35

10

50

Sodium (mg)

20

60

25

50

20

60

Potassium (mg)

80

200

60

160

60

160

Chloride (mg)

55

150

50

160

50

160

Selenium (g)

—

—

1.5

5.0

1

9

Fluoride (g)

—

—

0

60

—

60

Vitamin A (IU)

250

750

200

500

200

600

Vitamin D (IU)

40

100

40

100

40

100

Vitamin E (mg/␣TE/g PUFA)

0.7

—

0.5

5.0

0.5

5.0

Vitamin K (g)

4.0

—

1.0

25

4

25

Thiamine; vit B1, (g)

40

—

30

200

60

300

Riboflavin; vit B2, (g)

60

—

80

300

80

400

Niacin; vit B3, (g)

250

—

550

2000

300

1500

Pyridoxine; vit B6 (g)

35

—

30

130

35

175

Vitamin B12 (g)

0.15

—

0.08

0.7

0.1

0.5

Folic acid (g)

40

—

11

40

10

50

Pantothenic acid (g)

300

—

300

1200

400

2000

Biotin (g)

1.5

—

1.0

15

1.5

7.5

Vitamin C (mg)

8.0

—

6

15

10

30

ALA = ␣-linolenic acid; ESPGHAN = European Society of Pediatric Gastroenterology, Hepatology and Nutrition. Report of International Expert Group (IEG) for Codex Committee on Nutrition and Foods for Special Dietary Uses (CCNFSDU); FDA = U.S. Food and Drug Administration; LA = linoleic acid; LSRO = Life Sciences Research Organization for U.S. FDA.

 Table 10.4 Median weight (kg)/age and length (cm)/age of male and female children constituting the populations of the World Health Organization (WHO; predominantly breastfed) and Centers for Disease Control and Prevention (CDC; predominantly formula-fed) Growth Standard/Reference

studies [24, 25]

Weight for age

Length for age

Male

Female

Male

Female

Age (m)

WHO

CDC

WHO

CDC

WHO

CDC

WHO

CDC

0

3.3

3.5

3.2

3.4

49.9

52.7

49.1

51.7

1

4.5

4.9

4.2

4.5

54.7

56.6

53.7

55.3

2

5.6

5.7

5.1

5.2

58.4

59.6

57.1

58.1

3

6.4

6.4

5.8

5.9

61.4

62.1

59.8

60.5

4

7.0

7.0

6.4

6.4

63.9

64.2

62.1

62.5

5

7.5

7.6

6.9

7.0

65.9

66.1

64.0

64.4

6

7.9

8.2

7.3

7.5

67.6

67.9

65.7

66.1

12

9.6

10.5

8.9

9.7

75.7

76.1

74.0

74.4

24

12.2

12.7

11.5

12.1

87.1

86.9

85.7

85.4

36

14.3

14.4

13.9

13.9

96.1

95.3

95.1

94.2

48

16.3

16.3

16.1

15.9

103.3

102.5

102.7

101.3

60

18.3

18.5

18.2

18.0

110.0

109.2

109.4

108.0

that have been shown to be safe and suitable under ulations and general recommendations for rigorous the applicable food safety provisions of the act may be clinical trial design, conduct, and analysis.

used in infant formulas. The manufacturer also must The labels of infant formulas must include instruc-provide assurance that the formula meets the nutrient tions for use, including pictorial instructions; a state-content and quantity specifications as well as the nutri-ment warning against improper preparation or use; a ent quality standards of the act and demonstrate that statement cautioning that the infant formula should be all required nutrients are present and available at the used only as directed by a physician; and a “use by”

specified levels throughout the shelf life of the product.

date that ensures the formula will deliver no less than Finally, the manufacturer must demonstrate that the the quantity of nutrients stated on the product label formula contains no contaminant and that the concen-at that date. To comply with the World Health Orga-trations of required nutrients do not exceed the maxi-nization (WHO) Code for Marketing Infant Formulas mum level allowed.

[24], the label also must state that breastfeeding is the In some cases, exemptions from the nutrient spec-preferred method of feeding infants. Many infant for-ifications are permitted. These allow availability of formula labels also contain claims. These must be truthful mulas for feeding infants with special medical and and not misleading; however, there is no requirement dietary needs, for example, formulas for children with that label claims be approved by the FDA.

inborn errors of metabolism and formulas for low birth weight infants whose nutrient requirements are thought to differ from those of term infants.

Growth of formula-fed infants Infant formulas, as the sole source of nutrition, Most reports from industrialized countries indicate must contain all nutrients required to support nor-that weight and length gains of formula-fed infants are mal growth and development. Ordinarily, manufac-greater than those of breastfed infants. However, rates turers submit documentation that the formula, when of gain during the first few weeks to months of life gen-fed as the sole source of nutrients, supports normal erally are about the same in breastfed and formula-fed growth and development for approximately 60 days.

infants or are somewhat greater in breastfed infants.

The clinical studies are generally conducted in accor-Examples of early growth are illustrated in Table 10.4,

dance with specific recommendations for infant pop-which shows the median weight and length (height) **Section 2: Nutritional regulation and requirements for lactation and infant growth** Table 10.5 Weight and length gains of breastfed and ments for growth and development, as well as other formula-fed infants

health considerations. Thus, it is difficult to specify an **Length gain (mm/d ± SD)** age for introduction of complementary foods that is appropriate for all infants.

Males

Females

Complementary feeding

Interval Breastfed Formula-fed Breastfed Formula-fed An attempt to formulate guidelines for complemen-8–56 d 1.22 ± 0.16 1.28 ± 0.17

1.15 ± 0.17 1.2 ± 0.14

tary feeding was made recently by a group convened by 8–112 d 1.07 ± 0.18 1.13 ± 0.11

1.01 ± 0.11 1.04 ± 0.09

the American Dietetic Association and Gerber Products Company to formulate feeding recommendations for 6-to 24-month-old infants and toddlers [28].

Weight gain (g/d)

This group assumed that the nutrient needs of these **Males**

Females

children were equal to the Dietary Reference Intakes (DRIs) issued by the Food and Nutrition Board– **Interval Breastfed Formula-fed Breastfed Formula-fed** Institute of Medicine/Health Canada [29–34]. Thus, 8–56 d 37.1 ± 8.7

38.3 ± 7.0

31.7 ± 7.9

32.1 ± 6.5

recommendations concerning the amounts of nutri-8–112 d 29.8 ± 5.8

32.2 ± 5.6

26.2 ± 5.6

27.5 ± 4.9

ents needed by breastfed infants from complementary foods were estimated as the difference between for age at various ages of both males and females the content of each nutrient in the average intake of participating in the recent WHO Multicenter Growth human milk and the DRI for that nutrient. Examples of Reference Study [25], as well as the same data from this exercise for 6-to 8-month-old infants are shown in infants comprising the current WHO/Centers for Dis-

Table 10.6. This process is similar to that used to esti-ease Control and Prevention growth references [26].

mate the complementary food needed by children in The former group was primarily breastfed, and the developing countries [35].

latter was primarily formula-fed. Table 10.5 shows the Because the average intake of infant formula sup-median daily rates of increase in weight and length plies the amount of each nutrient needed for normal of more than 300 breastfed and formula-fed infants growth through the first 12 months of life, formula-fed studied during the 1980s at the University of Iowa [27].

infants do not require complementary foods to sup-Although the rates of gain in weight and length port normal growth. This is illustrated in Table 10.7,

of formula-fed and breastfed infants, overall, are not which was compiled in the same way as Table 10.6 but dramatically different, the small differences have given substituting the amounts of each nutrient in 708 ml rise, on one hand, to

arguments that the breastfed of a common cow's milk–based formula. Although infants' lower rates of gain indicate that breastfeeding formula-fed infants do not need complementary foods may be less than optimal and, on the other, to argu-to support normal growth, these foods are essential for ments that formula feeding is excessive and con-development of oromotor skills and the development tributes to subsequent development of obesity.

of familiarity with different flavors and textures. It is The differences or lack of differences described clear from Tables 10.6 and 10.7 that complementary here concerns infants in industrialized countries. In foods that meet the nutrient needs of breastfed infants less industrialized countries, a number of factors inter-are likely also to be adequate for formula-fed infants act to increase the variability of weight and length receiving appropriate volumes of formula.

gains. In these countries, formula feeding is often These exercises indicate that less than 50% of the dangerous because of overdilution of the formula, an recommended daily allowance for iron and zinc and unsafe water supply, lack of refrigeration, and other less than 50% of the adequate intake (i.e. the amount factors that are less common than in industrialized received by normally growing breastfed infants) for countries.

manganese, fluoride, vitamin D, vitamin B6, niacin, Most exclusively breastfed infants need additional vitamin E, magnesium, phosphorus, biotin, and thi-nutrients by 6 months of age, and some need them amin are met by the average intake of human milk earlier. Deciding when to start complementary foods from 6 to 8 months of age (708 ml). Thus, the comple-requires balancing the physiological and developmen-mentary foods chosen should be good sources of these **100**

tal readiness of the infant and the nutrient require-nutrients.

Chapter 10: Influences of timing and duration of formula feeding on infant growth Table 10.6 Calculation of nutrients needed from complementary foods by 6-to 8-month-old breastfed children **Intake from 708 ml Nutrient**

DRI (6–8 mo)

breast milk

Intake – DRI

% DRI needed

Energy

649 kcal/d

486 kcal/d

163 kcal/d

25%

Protein

9.9 g/d

7.4 g/d

−2.5 g/d

25%

Fat

30 g/d

22.5 g/d

−7.5 g/d

25%

Vit A

500 g/d

354 g/d

−146 g/d

29%

Vit C

50 mg/d

28.3 mg/d

−22 mg/d

44%

Vit D

5 g/d

0.39 g/d

−4.6 g/d

92%

Vit E

5 mg/d

1.6 mg/d

−3.4 mg/d

68%

Vit K

2.5 g/d

1.5 g/d

−1.0 g/d

40%

Thiamine

0.3 mg/d

0.15 mg/d

−0.15 mg/d

50%

Riboflavin

0.4 mg/d

0.25 mg/d

−0.15 mg/d

60%

Niacin

4 mg/d

1.1 mg/d

−2.9 mg/d

72.5%

Vit B6

300 g/d

66 g/d

−234 g/d

78%

Folate

80 g/d

60 g/d

−20 g/d

25%

Vit B12

0.5 g/d

0.7 g/d

0.2 g/d

0%

Pantothenic acid

1.8 mg/d

1.3 mg/d

−0.5 mg/d

28%

Biotin

6 g/d

2.8 g/d

−3.2 g/d

53%

Calcium

270 mg/d

198 mg/d

−72 mg/d

27%

Chromium

5.5 g/d

35.4 g/d

30 g/d

0%

Copper

220 g/d

180 g/d

−40 g/d

18%

Chloride

570 mg/d

297 mg/d

−273 mg/d

48%

Fluoride

500 g/d

11.3 g/d

−489 g/d

98%

Iodine

130 g/d

78 g/d

−52 g/d

40%

Iron

11 mg/d (RDA)

0.21 mg/d

−10.8 mg/d

98%

Magnesium

75 mg/d

25 mg/d

−50 mg/d

67%

Manganese

600 g/d

4.3 g/d

−596 g/d

99%

Phosphorus

275 mg/d

99 mg/d

−176 mg/d

64%

Potassium

700 mg/d

372 mg/d

−328 mg/d

47%

Selenium

20 g/d

14.2 g/d

−5.8 g/d

39%

Sodium

370 mg/d

127 mg/d

−243 mg/d

66%

Zinc

3 mg/d

0.85 mg/d

−2.15 mg/d

72%

DRI = Dietary Reference Intake; RDA = recommended daily allowance.

Because iron deficiency can result in cognitive and fortified infant cereals. A serving of 30 g of infant motor deficits, some of which may not be reversible cereal provides the daily iron requirement, and feeding [36], prevention of iron deficiency is particularly the cereal with vitamin C–rich foods (such as strained important. By about 6 months of age, most term fruits) helps ensure that the iron from the cereal will breastfed infants require an additional source of be absorbed. Formula-fed infants should receive only dietary iron to meet their iron requirement. Good iron-fortified formula, which also should be used for **101**

sources include meats, especially red meats, and iron-supplementing breastfed infants.

Section 2: Nutritional regulation and requirements for lactation and infant growth Table 10.7 Calculation of nutrients needed from complementary foods by 6-to 8-month-old formula-fed children **Formula**

Nutrient

DRI (7–12 mo)

intake (708 ml)

Intake – DRI

% DRI

Energy

649 kcal/d

474 kcal/d

−175 kcal/d

27%

Protein

9.9 g/d

10 g/d

–

–

Fat

30 g/d

25.5 g/d

−4.5 g/d

15%

Vit A

500 g/d

1423 g/d

923 g/d

0%

Vit C

50 mg/d

43 mg/d

−7 mg/d

14%

Vit D

5 g/d

7.1 g/d

2.1 g/d

0%

Vit E

5 mg/d

7 mg/d

2 mg/d

0%

Vit K

2.5 g/d

38 g/d

36.5 g/d

0%

Thiamine

0.3 mg/d

0.47 mg/d

0.17 mg/d

0%

Riboflavin

0.4 mg/d

0.7 mg/d

0.3 mg/d

0%

Niacin

4 mg/d

4.9 mg/d

0.9 mg/d

0%

Vit B6

300 g/d

285 g/d

−15 g/d

5%

Folate

80 g/d

71 g/d

−9 g/d

11%

Vit B12

0.5 g/d

1.2 g/d

0.7 g/d

0%

Pantothenic acid

1.8 mg/d

2.35 mg/d

0.55 mg/d

0%

Biotin

6 g/d

21 g/d

15 g/d

0%

Calcium

270 mg/d

370 mg/d

100 mg/d

0%

Chromium

5.5 g/d

26 g/d

210 g/d

0%

Copper

220 mg/d

430 mg/d

0.21 mg/d

0%

Chloride

570 mg/d

304 mg/d

−266 mg/d−

47%

Fluoride

500 g/d

–

–

–

Iodine

130 g/d

29 g/d

−100 g/d

77%

Iron

11 mg/d

8.5 mg/d

−2.5 mg/d

23%

Magnesium

75 mg/d

29 mg/d

−46 mg/d

61%

Manganese

600 g/d

24 g/d

−576 g/d

96%

Phosphorus

275 mg/d

199 mg/d

−76 mg/d

28%

Potassium

700 mg/d

516 mg/d

−154 mg/d

22%

Selenium

20 g/d

114 g/d

94 g/d

65%

Sodium

370 mg/d

130 mg/d

−240 mg/d

−2%

Zinc (mg)

3 mg/d

3.6 mg/d

0.6 mg/d

–

DRI = Dietary Reference Intake.

Both human milk and currently available infant low intakes are associated with signs and symptoms of formulas provide generous amounts of the essential deficiency (poor growth, scaly skin lesions, impaired fatty acids, linoleic acid, and ␣-linolenic acid. How-wound healing, impaired visual acuity) is not clear, ever, cow's milk, especially skim and low fat milk, has but to help ensure adequate intakes, cow's milk should very low levels of these fatty acids, and low linoleic not be introduced until after 1 year of age, and only acid intake has been documented in infants and tod-whole milk should be fed until at least 2 years of

dlers fed cow's milk [37]. The extent to which these age.

Chapter 10: Influences of timing and duration of formula feeding on infant growth There has been considerable concern that infants are that they should be breastfed for as long as possible receiving adequate amounts of linoleic and ␣-linolenic and should not receive complementary foods until 6

acids may also need a dietary source of the long-months of age. Until recently, it was recommended that chain polyunsaturated products of these fatty acids, for introduction of the major food allergens be delayed example, AA and DHA, particularly the latter. Because until after the first year of age and that introduction of human milk contains these fatty acids and formu-foods associated with "lifelong" sensitization (peanuts, las supplemented with them are available, intakes by tree nuts, fish, and shellfish) be delayed even longer.

breastfed infants and infants fed supplemented for-However, recent recommendations do not stress such mula are probably adequate through approximately caution.

1 year of age [38, 39]. It is not clear whether toddlers The parents' approach to child feeding is central to will benefit from supplements of these long-chain fatty the child's early feeding experience. The appropriate acids. Nonetheless, DHA-supplemented complemen-approach is often described as a division of responsibil-tary foods are now available.

ity between parent(s) and child. The parents' responsi-There is no convincing evidence that the order of bility is to set the environment and provide appropriate introduction of foods other than those rich in iron healthy foods, and the child's

responsibility is to decide is important. However, only one new food should be whether to eat and, if so, how much [40]. In this regard, introduced at a time, and others should not be intro-it is important to note that some foods must be pre-duced for 3 to 4 days to allow time for detection of any sented several times before they are finally accepted by difficulty with the newly introduced food.

the child. It also is important to avoid major encoun-Current recommendations for infants with a strong ters with the child if he or she continues to refuse a spe-family history of food allergy (i.e. those whose parents cific food, particularly one that has no unique nutri-or siblings have or had significant allergic reactions) tional quality.

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Section 2

Nutritional regulation and requirements for lactation and

Chapter

infant growth

11**Maternalandoffspringbenefitsof**

breastfeeding

Alison C. Tse and Karin B. Michels

Introduction

Infant feeding practices have undergone changes dur—
maternal health have only recently been recognized.
ing the past century, especially in the developed world.
Reported child benefits include decreased risks of
Commercially prepared infant formula first became
infections (including gastrointestinal and lower res—
available in the late 19th century, supplementing the
piratory infections), lower risk of obesity, and bet—
range of choices available and eventually replacing
ter cognitive development. Breastfeeding has also
cow’s milk as a substitute for breast milk. In the
been linked to decreased incidence of maternal breast
first half of the 20th century, bottle-feeding was more
cancer and increased postpartum weight loss. More
popular among women of higher socioeconomic sta—

recently reported maternal benefits include decreased

tus (SES), in part as a result of marketing of breast—

risks of Type II diabetes (TIIDM) and cardiovascular

milk substitutes as equal, if not superior, to maternal

disease (CVD). In 2000, the U.S. Department of Health

milk [1]. Breastfeeding is currently more common Services reported breastfeeding rate goals of 75% for among white (compared with black), older, more edu—

initiation, 50% at 6 months, and 25% at 12 months by

cated, and higher-income women in the United States

2010 [6].

[2] (Table 11.1). According to the U.S. Centers for Dis-In evaluating studies on the benefits of breast-ease Control and Prevention (CDC), 11.3% of moth—

feeding for maternal and child health, several method—

ers exclusively breastfeed at 6 months and 20.9% of

ological issues must be considered. Because it is

mothers breastfeed (either exclusively or partially) at

not without ethical concern to randomize infants

12 months [2]. Breastfeeding rates in the United States to breastfeeding or formula, most of the studies increased substantially during the 1970s and reached

are observational, mostly of cohort and case-control

a peak in the early 1980s. Following a general trend of

design. A cohort study is composed of a group of indi—

a decline from the early to late 1980s and a substantial

viduals from a population who are defined according

increase into the new millennium, breastfeeding rates

to their exposure levels at baseline and followed

in the United States appear to be leveling off [3] (Fig.

over time for the occurrence of outcomes of inter-

11.1).

est [7]. However, cohort studies are costly and time-Breast milk is higher in lactose and lower in protein consuming because of the large number of participants

than cow's milk [1]. Although the protein in cow's milk who must be followed for a long duration. Conver-is predominantly casein, the major protein in human sely, in a case-control study, individuals are defined by

milk is whey. In addition to containing more choles—

whether they have the disease of interest. Exposure his—

terol than cow's milk, human milk differs greatly in the

tories are then compared between cases and controls

composition of fatty acids [4]. Compared with cow's who are representative of the population from which milk, human milk contains fewer short-chain polyun—

cases have arisen. Although case-control studies are

saturated and saturated fatty acids but substantially

less expensive and time-consuming, bias may be intro—

more long-chain polyunsaturated fatty acids (LCPU—

duced if participants associate their case status with a

FAs). Early formulas were high in protein and butter—

lack of breastfeeding or if controls are not representa—

fat, but most currently available formulas are designed

tive of the source population for cases.

to more closely approximate breast milk's nutrient

An inherent limitation of observational studies on

content [1, 5].

breastfeeding is that the choice to breastfeed may

Although the benefits of breastfeeding for the

be dependent on demographic or lifestyle factors that

child's health have long been suspected, benefits for

also are related to health status. To minimize bias in

 Table 11.1 Estimated percentage of U.S. infants born in 2004 who were ever breastfed, exclusively breastfed through age 6 months, and breastfed through age 12 months, by selected sociodemographic characteristics in the National Immunization Survey [6]

Ever

Exclusive breastfeeding

Breastfeeding

breastfeeding

through age 6 monthsa

at 12 months

Characteristics

(%)

(%)

(%)

U.S. overall

73.8

11.3

20.9

Race/Ethnicity

White, non-Hispanic

73.9

11.7

20.8

Hispanic

81.0

11.6

24.1

Black, non-Hispanic

56.2

7.5

11.9

Asian or Pacific Islander

81.7

15.8

29.1

American Indian or Alaska

77.5

11.4

24.3

Native

Maternal age at birth (yr)

Ↄ20

55.8

6.1

8.6

20–29

69.8

8.4

16.7

≥ 30

77.9

13.8

24.9

Education

Ↄ High school

67.7

9.1

18.5

High school

65.7

8.2

16.8

Some college

75.2

12.3

18.5

College graduate

85.3

15.4

28.2

Marital status

Married

79.6

13.4

24.5

Unmarried

60.0

6.1

12.4

Income: poverty ratio

Ↄ 100

65.9

8.3

18.6

100–184

70.8

8.9

16.6

185–349

75.1

11.8

21.3

≥ 350

81.5

14.0

23.6

a Exclusive breastfeeding is defined as only breast milk (no solids, water, or other liquids).

epidemiological studies, care must be taken to measure

tial and exclusive breastfeeding in many studies. The

adequately and control for such confounding factors

World Health Organization (WHO) defines exclusive

[7]. However, it is difficult to capture these differences breastfeeding as follows: “The infant has only breast completely, and residual or unmeasured confounding

milk from his/her mother or a wet nurse, or expressed

may persist. Second, differences between the assess—

breast milk, and no other liquids or solids with the

ment and definition of breastfeeding make compar—

exception of drops or syrups consisting of vitamins,

isons across studies difficult. In most studies, breast—

mineral supplements, or medicine” [8].

feeding is assessed as a dichotomous variable (i.e. ever

The purpose of this chapter is to evaluate criti—

vs. never) and/or as a lifetime duration in months. Few

cally some of the reported infant and maternal ben—

studies have attempted to assess the impact of exclu—

efits of breastfeeding. For each topic, we start by

sive breastfeeding, and a significant gap in the litera—

briefly reviewing the relevant mechanisms and then

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ture stems from a lack of differentiation between par—

focus on the epidemiological evidence, evaluating the

Section 2: Nutritional regulation and requirements for lactation and infant growth In-hospital Figure 11.1 U.S. breastfeeding rates,

At 6 months of age

1965–2006, in the Ross Laboratories

Mothers' Survey [3].

80

70

ed 60

50

40

30

20

% infants breastf

10

0

1965

1970

1975

1980

1985

1990

1995

2000

2005

year

methodological strengths and limitations. We do not

1.37). Adjusting for the same confounders and mater—

address special issues such as HIV transmission via

nal smoking during pregnancy, no associations were

breast milk, which is beyond the scope of this chapter.

found between assignment to breastfeeding intervention and two or more respiratory tract infections (OR

= 0.87, 95% CI 0.62–1.37) or hospitalization for respi-

Benefits for child

ratory tract infection (OR = 0.85, 95% CI 0.57–1.27).

Observational data from well-defined cohorts in

Immune function

developed countries also support the hypothesis of

Breast milk contains several components that proa protective association between breastfeeding and

mote passive and active immunity [9]. These factors infections. The association of breastfeeding with onset are either present in low levels or absent in formula.

of otitis media was examined in a prospective cohort of

Immunoglobulins (IGs), including IgA antibodies,

1013 infants in a health maintenance organization in

directed at microbes in the maternal environment, are

Arizona [11]. After adjustment for sex, day-care atten-transferred from the mother to the infant through dance, presence of siblings at home, maternal smok —

breast milk. Lactoferrin, an iron-binding protein

ing, and parental history of hay fever, infants who were

present at high levels in human milk, is relatively resis—

breastfed for 6 months or longer had decreased risks

tant to enzymatic degradation and is microbicidal and

of both acute otitis media (OR = 0.61, 95% CI 0.40–

anti-inflammatory. Oligosaccharides present in breast

0.92) and recurrent otitis media (OR = 0.39, 95% CI

milk may prevent colonization of mucous membranes

0.21–0.73) during the first year of life when compared

by competing with microbes for receptors.

with non-breast-fed infants.

Perhaps the strongest evidence for an associa—

The associations of current and past breastfeeding

tion between breastfeeding and gastrointestinal infec—

with hospitalization for diarrheal and lower respi—

tions comes from the Promotion of Breastfeeding

ratory tract infections (LRTIs) were examined in

Intervention Trial (PROBIT), a randomized trial of

a nationally representative cohort of 15 980 British

17 046 infants followed for 1 year in Belarus, an eastern

infants born between 2000 and 2002 [12]. In the first European country [10]. Matched on several potential 8 months of life, exclusively breastfed infants (but not confounders, study hospitals and their correspond—

partially breastfed infants) had a lower risk of devel—

ing clinics were assigned to a breastfeeding promo—

oping diarrhea compared with infants who were not

tion intervention or no intervention. Adjusting for

breastfed, after adjustment for infant’s age, maternal

birth weight and number of children in the house—

age, mode of delivery, and maternal education (OR for

hold, infants in the intervention group had a lower

exclusively breastfed = 0.37, 95% CI 0.18–0.78; OR

risk of gastrointestinal infection (odds ratio [OR] =

for partially breastfed = 0.63, 95% CI 0.32–1.25). Sim—

0.60, 95% CI [confidence interval] 0.40–0.91) but not

ilarly, exclusively breastfed infants (but not partially

hospitalization for gastrointestinal tract infection dur—

breastfed infants) had a lower risk of LRTI, which

ing the first year of life (OR = 0.92, 95% CI 0.62–

was defined as chest infection or pneumonia, but not

 wheezing or asthma, after adjusting for the same con-lower rates of weight and fat mass gain compared with founders (OR for LRTI in exclusively breastfed =

formula-fed infants during the first year of life, which

0.66, 95% CI 0.47–0.92; OR for partially breastfed =

may be explained by lower total energy and protein

0.69, 95% CI 0.47–1.00). The protective effect of breast—

intakes in breastfed infants compared with formula-feeding on both types of infections did not appear to

fed infants [17]. Rapid growth during early child-persist following cessation of breastfeeding.

hood may have adverse implications for growth and

The relation between infant feeding practices and

body mass later in life [18]. Compared with breastfed infections in the developing world deserves special infants, formula-fed infants have higher serum con—

attention because of the substantial proportion of

centrations of insulin-like growth factor 1 (IGF-1)[19]

neonatal deaths due to infections, which in part can be

and higher plasma concentrations of insulin, which

attributed to limited access to clean, nutritious alter—

stimulates greater deposition of body fat and could

natives to breast milk. In a recent meta-analysis of six

lead to insulin resistance [20]. Formula-fed infants studies conducted in Brazil, the Gambia, Ghana, Pak-have lower serum concentrations of leptin, a hormone istan, the Philippines, and Senegal, infants who were

that regulates food intake and energy balance [21].

not breastfed had increased risks of death during the

Breastfeeding may also foster maternal feeding styles

first 6 and 12 months of life due to diarrhea (6 months

that are less controlling and more responsive to infant

OR = 6.1, 95% CI 4.1–9.0; 12 months OR = 1.9, 95%

cues of hunger and satiety, leading to the development

CI 1.2–3.1) and acute respiratory infection (ARI; 6

of greater self-regulation of energy intake and ability

months OR = 2.4, 95% CI 1.6–3.5; 12 months OR =

to respond to internal appetite cues [22].

2.5, 95% CI 1.4–4.6) after adjustment for maternal

Observational studies on the association between

education [13]. In a clustered randomized trial of breastfeeding and obesity are subject to confound-a community-based promotion of exclusive breast-ing by SES. In many early studies, differences in SES

feeding in 1115 infants in Haryana, India, infants in

between breastfed and non-breast-fed children were

the intervention group had a significantly lower 7-day

not adequately accounted for. In a meta-analysis of 28

diarrhea prevalence at 3 months (OR = 0.64, 95% CI

observational studies, the unadjusted summary esti—

0.44–0.95) and 6 months (OR = 0.85, 95% CI 0.72–

mate suggested that having been breastfed was pro—

0.99) after adjusting for maternal working status [14].

tective against obesity measured at varying time points

Observational data from developed countries sug—

later in life (range of mean age of evaluation of obe—

gest that breastfeeding decreases the risks of gastroin—

sity = 0.5–33 years; OR = 0.87, 95% CI 0.85–0.89)

testinal and LRTIs and otitis media [11, 12]. In devel-

[23]. The association did not differ by the age at which oping countries, an association between breastfeeding obesity was measured. However, the crude summary

and decreased risks of diarrheal and ARI mortality in

estimate for the association in six studies that assessed

the first year of life has been suggested. Given the high

maternal smoking, SES, and parental body mass index

mortality in developing countries from infections early

(BMI; OR = 0.86, 95% CI 0.81–0.91) attenuated greatly

in life, these results may have substantial public health

when all three of these confounders were adjusted for

implications [13, 14]. Additionally, the high morbidity (OR = 0.93, 95% CI 0.88–0.99).

in developed countries due to infections early in life

Evidence from the largest study to date, the Nurses'

suggests that increasing breastfeeding rates may have

Health Study II (NHS II), suggests that any inverse

a large public health impact [12].

association between having been breastfed and adiposity in childhood is not maintained into early or

mid-adulthood [24]. The association between duration Overweight and obesity of breastfeeding and overweight and obesity across

On the basis of early epidemiological reports on an

the life course was examined in a cohort of 35 500

inverse link between breastfeeding and childhood

U.S. female nurses for whom breastfeeding informa—

body mass, public health organizations such as the

tion was obtained from their mothers. Several indi—

CDC and lay organizations such as La Leche League

cators of SES and other confounders were controlled,

International, an organization that promotes breast—

limiting the extent of residual confounding. Compared

feeding through mother-to-mother support, have rec—

with women who were breastfed exclusively for less

ommended breastfeeding to prevent pediatric obe—

than 1 week, women who were exclusively breastfed

sity and overweight [15, 16]. Breastfed infants have for 6 months or longer (but not shorter durations) **Section 2: Nutritional regulation and requirements for lactation and infant growth** Table 11.2 Associations of exclusive breastfeeding duration in infancy with early life body shape and adult overweight and obesity in the Nurses' Health Study II [23]

Body shapea

Obesityb

Overweightb

Age 5

Age 10

Age 18

Adulthoodc

Age 18

Adulthoodc

None or ↄ 1 week

1

1

1

1

1

1

1 week–3 months

1.00 (0.86–1.16)

1.05 (0.92–1.20)

1.09 (0.87–1.37)

0.98 (0.89–1.08)

0.95 (0.83–1.09)

1.01 (0.93–1.10)

3–6 months

0.98 (0.81–1.19)

1.12 (0.95–1.31)

0.86 (0.63–1.17)

1.03 (0.92–1.16)

1.01 (0.82–1.18)

0.99 (0.90–1.10)

Ć9 months

0.81 (0.65–1.01)

0.93 (0.77–1.11)

1.01 (0.73–1.39)

0.94 (0.83–1.07)

1.12 (0.94–1.33)

0.98 (0.87–1.10)

p for trend

0.1

0.92

0.72

0.63

0.35

0.75

a OR for highest vs. lowest category, adjusted for age at return of questionnaire, year of birth, maternal pre-pregnancy weight, maternal pregnancy weight gain, birth weight, gestational age, maternal education, paternal education, maternal occupation, paternal occupation, and home ownership. NHS II participants were asked to recall their body shape at ages 5 and 10 using a nine-level figure drawing, which was validated previously.

b OR adjusted for the same as above and age at menarche, parity, age at first birth, physical activity, alcohol consumption, smoking, daily energy intake, menopausal status, income, and husband's education. Body mass index (BMI) was calculated as height in meters squared divided by weight in kilograms. Obesity was defined as a BMI greater than or equal to 30.

c At end of follow-up in 2001 (age range: 37–54 years). Overweight was defined as a BMI of greater than or equal to 25, but less than 30.

had a slightly decreased risk of high adiposity at age

early brain development [26, 27]. Commercially pre-5 after adjustment for maternal characteristics, par-pared formulas supplemented with DHA and AHA ticipant characteristics, and several indicators of SES

levels comparable to those of human milk are now

(Table 11.2). However, no reduction in risk of high adi-available [26].

posity at age 10 was seen in women who were exclu—

In a meta-analysis of 11 observational studies,

sively breastfed for any duration. Moreover, women

children who were breastfed had cognitive function

who were exclusively breastfed in infancy for any

scores that were 5.32 points higher than those of

duration did not have reduced risks of overweight or

non-breast-fed children at ages 6 months to 15 years

obesity at age 18 or later in adulthood.

(95% CI 4.51–6.13) in the unadjusted estimate [27].

The association between having been breastfed

However, following adjustment for several covariates,

with obesity and overweight may be largely explained

the summary effect estimate attenuated to a differ—

by lifestyle factors associated with socioeconomic gra—

ence of 3.16 points (95% CI 2.35–3.98) between breast—

dients [23, 24]. Even if the association of breastfeeding fed and non-breast-fed children, suggesting that other with childhood and adolescent obesity is real, the effect

unmeasured confounders might explain the asso—

size likely is small, and the role of exclusive versus par—

ciation. Although the authors of the meta-analysis

tial breastfeeding needs to be clarified [23, 24]. The attempted to minimize the effects of confounding by existing data suggest that breastfeeding may some—

including only studies that adjusted for at least five

what reduce the risk of child overweight and obesity,

covariates, many of the studies did not adjust for

although differences in body mass do not appear to

maternal intelligence and/or child stimulation.

persist into adulthood [24].

However, given that most studies have been conducted in recent times and the known increased prevalence of breastfeeding in higher socioeconomic strata,

Cognition

mothers of breastfed children in many studies may

Compared with formula, breast milk is hypothesized

have tended to provide a more cognitively stimulating

to foster improved cognitive development through the

environment [28–30]. Additionally, mothers of breast-superiority of its nutrients. Breastfed infants have fed children may have been more likely to have higher

higher docosahexaenoic acid (DHA) concentrations

IQs, which may also have been associated with their

in their cerebral tissues than bottle-fed infants [25].

child's IQ [28–30]. Therefore, adequate adjustment for Breast milk may support cognitive development by confounding needs to be made, but differences in SES

providing LCPUFAs, including DHA and arachidonic

and the home environment are difficult to control

110

acid (AA), which are hypothesized to be crucial for

completely.

Chapter 11: Maternal and offspring benefits of breastfeeding The association between duration of breastfeeding [35]. Breastfeeding, as opposed to formula-

feeding, and child development scores, with simultaneous may also protect against insulin resistance [20, 21] and adjustment for positive parenting practices, maternal obesity later in life [23], although the magnitude of the IQ, and other important covariates, has been examined association between infant feeding and obesity is likely

in at least three prospective cohort studies [28–30]. In small [24]. Blood pressure has been commonly investi-all three studies, an initial association vanished after gated as a surrogate for CVD. The association between

adjusting for markers of maternal cognition and the

breastfeeding in infancy and blood pressure later in

home environment.

life (ranging from age 1 to 60 years) was examined in

In summary, higher cognition scores in children

17 503 participants in a meta-analysis of 14 studies

who have been breastfed may largely be attributable

[36]. Compared to non-breast-fed participants, breast-to confounding. In particular, important differences fed participants had a lower mean systolic blood pres—

in SES, child stimulation, and maternal intelligence

sure (mean difference = –1.4 mmHg, 95% CI –2.2

between mothers who do and do not breastfeed may

to –0.6). However, publication bias and confound—

account for the association [28–30]. Because it is inhering were suggested by subsequent analyses and are ently difficult to control for such differences, studies on

compelling explanations for any observed association

the association between breastfeeding and child cog—

between breastfeeding and blood pressure.

nition must be interpreted with caution.

Breast cancer

Asthma

Breastfeeding could hypothetically increase the risk of

Breast milk has been suggested to protect against

breast cancer by transmitting an oncogenic virus from

childhood asthma by promoting gastrointestinal mat—

mother to child [37]. In contrast, other hypothesized uration and decreasing infant exposure to foreign mechanisms suggest that breastfeeding might pro—

dietary antigens, thereby decreasing the risk of sensitect against the development of breast cancer. Com—

tization [31]. Breast milk may also provide protection pared with formula-fed infants, breastfed infants have against lower respiratory tract infections, which may

lower levels of circulating IGF-1[19] and lower rates of decrease inflammatory responses and prevent pheno-weight and fat mass gain during the first year of life typic changes within the lungs and hyperreactivity to

[17], both of which may decrease the risk of breast airborne stimuli later in life. In a meta-analysis of cancer [38]. Reports from the Boyd Orr Cohort, a 12 prospective studies, which included 8183 children prospective cohort of 4999 British participants born

aged 1.5 to 8.4 years, children who were breastfed for 3

between 1918 and 1939, and the NHS I and II all sug—

months or longer had a decreased risk of asthma com—

gested no associations of either having been breastfed

pared with children breastfed less than 3 months (OR

or the duration of having been breastfed with risk of

= 0.70, 95% CI 0.60–0.81) [32]. The association was breast cancer later in life [38, 39]. In the NHS, no asso-stronger in children with a history of atopy (OR = 0.52, ciation was found when the analysis was restricted to

95% CI 0.35–0.79) than in children without family his—

women with a maternal history of breast cancer.

tory of atopy (OR = 0.73, 95% CI 0.62–0.86). However,

only about half of the studies controlled for confound—

Type I diabetes

ing, and separate crude and adjusted estimates were

Breastfeeding may decrease the risk of Type I diabetes

not computed and compared to examine the role of

(TIDM) by delaying the introduction of cow's milk

confounding. More recently published studies in older

into the diet and preventing the development of -cell

children have been equivocal, with one suggesting no

autoantibodies [40]. Growth factors, cytokines, and association between breastfeeding and asthma at age other immunomodulatory factors present in breast

14 [33], and another reporting an increased risk from milk may also prevent the

development of TIDM by ages 9 to 26 in children breastfed for 4 weeks or longer

promoting the immunological maturity of the intesti—

versus 4 weeks or less [34].

nal mucosal tissues of the infant [41]. In a meta-analysis of 14 studies, children who were breastfed Cardiovascular disease

for less than 3 months had an increased risk of TIDM

Breast milk contains LCPUFAs [26], which form an compared with children who were breastfed for 3

111

important component of the vascular endothelium

months or longer (OR = 1.23, 95% CI 1.12–1.35) [42].

Section 2: Nutritional regulation and requirements for lactation and infant growth However, all of the studies had a case-control design 19 to 30 months (relative risk [RR] = 0.89, floating

and an overwhelming majority relied on maternal

standard error = 0.025). A significant limitation of this

recall of infant diet. Prospective studies on the asso—

meta-analysis was that it excluded some of the largest

ciation of breastfeeding duration and islet autoanti—

studies for no apparent reason. Furthermore, the vast

bodies in young, genetically predisposed children have

majority of studies had a case-control design, which is

been conflicting [43–45].

prone to bias.

At least three prospective studies (including two

Type II diabetes

cohort studies and one nested case-control study) are

available on the association between cumulative lac—

Breastfeeding may decrease the risk of TIIDM by protation duration and breast cancer. An association was

tecting against insulin resistance [20, 21] and lowering found for extended durations only in a prospective the risk of obesity [23, 46], although the association cohort of 252 678 parous textile workers in Shanghai, between breastfeeding and obesity is likely small [24].

China, who were aged 39 to 72 at the end of follow-up

The association of having been breastfed with risk of

[52]. After adjusting for parity and age, having lactated TIIDM was examined in a meta-analysis of 76 744 ado-for more than 3 years (but not shorter durations) was lescents and adults from seven studies (including six

associated with reduced risk of breast cancer (RR for

cohort studies) [46]. Participants who were breastfed 37–48 months = 0.67, 95% CI 0.47–0.94; RR for ≥ 49

in infancy had a lower risk of TIIDM later in life (OR =

months = 0.61, 95% CI 0.43–0.87).

0.61, 95% CI 0.44–0.85). No evidence for confounding

In contrast, no association was found for any dura—

existed in the three studies that measured and adjusted

tion of lactation and breast cancer in an NHS analysis

for birth weight, parental diabetes, SES, and individual

of 89 887 U.S. parous nurses born from 1921 to 1945

or maternal body size. Further studies are needed to

and followed from 1986 to 1992 [53]. After adjusting examine the role of duration and exclusivity of breast-for age, parity, age at first birth, age at menarche, and feeding in the risk of TIIDM.

other confounders, no association was found between

Benefits for mother

categories of lactation duration and breast cancer for

either premenopausal (RR ≥ 24 months = 0.90, 95%

CI 0.53–1.54) or postmenopausal women (RR for ≥ 24

Breast cancer

months = 1.21, 95% CI 0.96–1.54). However, only 6%

Lactation may decrease the risk of maternal breast

of the study population lactated for extended durations

cancer by enhancing the differentiation of epithe-

(i.e. ≥ 24 months).

lial cells in the mammary duct [47]. Lactation for In an Icelandic case-control study nested within longer durations may also lower the number of lifetime

a cohort of 80 219 women aged 20 to 90 years, par—

ovulations, which has been hypothesized to decrease

ticipants who had no history of breastfeeding were

breast cancer risk [48], although the role of cumu-excluded from a postpublication analysis because of lative number of ovulatory cycles in the etiology of

concerns that an underlying medical condition may

breast cancer has been questioned [49]. The excretion have increased their breast cancer risk [54]. In that of carcinogens such as organochlorines through breast analysis, in which lactation for 1 to 4 weeks was des—

milk may decrease the risk of maternal breast cancer

ignated as the reference group, only women who lac-

[50].

tated for more than 105 weeks had a decreased risk

The association between lifetime duration of lac—

of breast cancer (OR for ≥ 105 weeks = 0.56, 95%

tation and incidence of breast cancer was examined

CI 0.35–0.89). The association was stronger in women

in a meta-analysis of 147 275 women from 47 stud—

diagnosed before age 40 (OR for 53–104 weeks = 0.17,

ies [51]. Adjusting for study, age, parity, age at first 95% CI 0.04–0.66; OR for ≥ 105 weeks = 0.23, 95% CI birth, and menopausal status, the risk of breast can—

0.02–2.17) than in women diagnosed after age 39 (OR

cer decreased by 4.3% for each 12-month increase in

for 53–104 weeks = 0.94, 95% CI 0.64–1.37; OR for ≥

lifetime duration of lactation (95% CI 2.9–5.8). The

105 weeks = 0.62, 95% CI 0.38–0.99).

magnitude did not differ by parity, age at birth of first

The epidemiological literature thus suggests that

child, age at diagnosis, family history of breast cancer,

if lactation affects maternal breast cancer risk, pro—

or menopausal status. The benefits of breastfeeding

longed lifetime durations would be required [52, 54].

did not become substantial until women breastfed for

This association was found in combined analyses

of both premenopausal and postmenopausal women, to postpartum was examined in a prospective cohort

although the association appeared to be stronger in

of 1538 primiparous and 2810 biparous participants

younger women [54]. Even so, the results must be in the NHS II who gave birth to a child between 1990

interpreted with caution because the association may

and 1991 [61]. After adjustment for age, physical activ-be due to an underlying morphological breast struc-ity in 1989, and physical activity change from 1989

ture that simultaneously increases risk of breast can—

to 1991, mothers who exclusively breastfed for 1 or

cer and leads to inadequate milk supply [53]. Future more months gained approximately 1 kg more com-studies should address the risk of breast cancer among pared with mothers who never breastfed. Despite the

women who cannot lactate versus women who choose

relatively large sample size, there were several limita—

not to breastfeed. Involution after lactation is a highly

tions to the NHS II analysis. First, the authors had to

coordinated apoptotic process that may lead to malig—

rely on the difference in weight following delivery rela—

nant transformation if not regulated properly [55].

tive to pre-pregnancy weight, making it difficult to dif—

How this may affect women who cannot lactate,

ferentiate between weight gain during pregnancy and

women who choose not to breastfeed, and women

weight change postpartum. Because women who gain

who use medication to suppress lactation needs to be

more weight during pregnancy also lose more weight

established. More research is also warranted in popu—

postpartum, weight gain during pregnancy would have

lations for whom extended durations of lactation are

to be adjusted for to assess the association between lac—

common to clarify the role of age at diagnosis (i.e.

tation and postpartum weight loss [58, 62]. Addition-premenopausal vs. postmenopausal) and exclusivity of ally, energy intake was not adjusted for, so that this

breastfeeding.

particular analysis addressed the joint effects of lactation and differences in maternal caloric intake between

breastfeeding and non-breast-feeding mothers.

Postpartum weight loss

Conversely, an association between lactation dura—

A commonly held belief is that lactation helps moth—

tion and postpartum weight loss was found in at least

ers to lose weight more quickly postpartum. Accord—

two small prospective cohort studies in which the

ing to a La Leche League publication, breastfeeding

authors measured actual postpartum weight change

may help some women to lose weight by mobilizing fat

and accounted for dietary habits. In a prospective

stores [56]. Lactation comes at a substantial metabolic cohort of 46 California women, mothers who lac-cost that translates into an increased energy expen-tated for at least 12 months lost 2.0 kg more between diture ranging from 595 to 670 k/cal day during the

1 and 12 months postpartum compared with moth—

first 6 months postpartum [57]. However, in devel-ers who lactated for less than

3 months, independent oped countries, where unlimited access to food is com—

of SES, age, ethnicity, maternal anthropometry, and

mon, nursing mothers may be less likely to restrict

infant sex and birth weight (–4.4 ± 3.4 kg vs. –2.4 ±

their energy intake due to fears of impairing the ability

3.0 kg) [62]. Notably, women who intentionally dieted to produce milk [58]. Additionally, an increase in pro-were excluded from this study. In another prospective lactin during lactation may lead to increased appetite

cohort study (n = 56), conducted in Louisiana, moth—

and increased energy intake in lactating mothers [59].

ers who lactated consumed significantly more kilo—

In a randomized trial of Honduran women, 141

calories than mothers who did not lactate (2055 ± 435

primiparous mothers of term normal-weight infants

kcal vs. 2005 ± 515 kcal) [63]. Women who exclu-who exclusively breastfed for the first 4 months were sively breastfed for 6 months lost significantly more

randomized to exclusive breastfeeding or supple—

weight from 3 to 6 months postpartum (–1.29 ± 0.64

menting with solid foods [60]. Women randomized to kg) compared with mothers who partially breastfed exclusive breastfeeding lost significantly more weight

(–0.82 ± 0.65 kg) or did not breastfeed (–0.16 ±

between 4 and 6 months postpartum compared with

0.85 kg) after adjusting for maternal age, parity, pre—

women randomized to supplementation (–0.5 ± 1.6 vs.

pregnancy weight, energy intake, and energy expendi-

–0.1 ± 0.8 kg). However, these results may not be gen—

ture exclusive of lactation.

eralizable to industrialized nations because of unlimIn conclusion, null or small effect estimates have

ited access to food in developed countries.

been found in most studies in which the associa—

The association between duration of exclusive

tion between duration of lactation and postpartum

breastfeeding and weight change from pre-pregnancy

weight change was examined [62, 63]. Despite the high **Section 2: Nutritional regulation and requirements for lactation and infant growth** metabolic burden of lactation, increased energy intake glucose metabolism [64, 65] and decreased inci-in breastfeeding mothers remains the principal expla-dence of TIIDM [67], which may lower the risk of nation for these findings. In studies in which an asso-CVD. Lactation may also decrease the risk of CVD

ciation was found, the magnitude was small.

through improved lipid metabolism. Higher levels of

high-density lipoprotein (HDL) have been reported

Diabetes

in lactating women when compared with nonlactating women [68]. It has been

hypothesized that an Lactation may affect the risk of maternal diabetes increased demand of triglycerides in the lactating

through improvements in insulin and glucose home—

breast may be met by increased mobilization of very

ostasis. Compared with nonlactating mothers, lac—

low-density lipoproteins toward the mammary gland

tating mothers have higher total energy expendi—

and the transfer of surface remnants to HDL.

ture, higher carbohydrate utilization, and lower fasting

The association between lactation and CHD has

insulin levels [64, 65]. Lactation may lead to decreased been examined in only one study. In the NHS, the asso-insulin resistance through preferential mobilization of ciation between duration of lactation and incidence of

glucose to the mammary gland for milk production

myocardial infarction (MI) and cardiac sudden death

[66].

was analyzed in a prospective cohort of 92 648 parous

In the NHS II, the association between lifetime

women followed for 16 years from 1986 [69]. After duration of exclusive breastfeeding and incidence of adjustment for age, parity, early adult adiposity, fam—

TIIDM was examined in more than 73 000 U.S. parous

ily history, smoking, diet, exercise, and other con—

nurses who were born between 1946 and 1965 and

founders, women who had lactated for 23 months or

followed for 12 years from 1980 [67]. After adjusting more had a lower risk of developing MI and sud-for parity, BMI at age 18, diet, physical activity, and den death compared with women who did not lactate

other established confounders, each additional year of

(RR = 0.81, 95% CI 0.67–0.98). However, no decreased

exclusive breastfeeding over the lifetime was associ—

risk of MI and sudden death was seen for women who

ated with a 12% decrease in risk of developing TIIDM

lactated for shorter durations (Ć11–23 months RR =

(95% CI 6%–18%).

0.91, 95% CI 0.80–1.04).

Similarly in the NHS, the association between life—

The association between lactation and hyperten—

time duration of breastfeeding (whether exclusive or

sion has also been examined in only a few studies. In

not) and incidence of TIIDM was examined in more

a prospective cohort of 106 584 parous Korean women

than 83 000 U.S. parous nurses born from 1921 to 1945

followed for 6 years, lifetime lactation duration of as

and followed for 14 years from 1986 [67]. In an ana-little as 1 to 6 months

decreased the risk of hyperten-lytic model similar to that used in the NHS II analysis, sion by 10% (95% CI 0.87–0.93) independent of age,

each 1-year increase in lifetime duration of lactation

parity, obesity, smoking, alcohol use, physical exer—

was associated with a 4% decrease in risk of TIIDM

cise, and age at first pregnancy (RR for 4–6 months =

after adjustment for confounders (95% CI 1%–8%).

0.90, 95% CI 0.85–0.96; RR for 7–12 months = 0.92,

A robust association between lactation and TIIDM

95% CI 0.87–0.98; RR for 13–18 months = 0.93, 95%

was found in two studies [68]. However, results must CI 0.86–0.99) [70]. In the Coronary Artery Risk and be interpreted with caution and confirmed in fur- Development in Young Adults Study (CARDIA), 109

ther follow-up studies. Although clinical studies have

parous U.S. women aged 24 to 42 years were fol—

found evidence to support a protective effect of lacta—

lowed for 3 years during which an interim conception

tion on glucose homeostasis [62, 65], failure to pro-and birth occurred. In CARDIA, no significant differ-duce adequate milk for breastfeeding may be a marker ences in change in systolic blood pressure and change

for impaired glucose or lipid homeostasis or other

in diastolic blood pressure from preconception levels

health-related behaviors that may affect glucose or

existed between mothers who breastfed and weaned

lipid homeostasis.

their child and mothers who did not breastfeed [71].

Notably both the Korean Women's Health (mean =

Cardiovascular disease

32.2 years) and the CARDIA cohorts both consisted

Lactation may affect several risk factors for coro—

of relatively young women and had relatively short

nary heart disease. Extended duration of lactation

follow-up periods so that any long-term impact on

has been independently associated with improved

blood pressure could not be evaluated.

Chapter 11: Maternal and offspring benefits of breastfeeding Lactation may improve maternal cardiovascu-benefit for maternal breast cancer may be limited to lar health, although few studies exist. It remains

the extended durations of breastfeeding more com—

unclear whether the changes in blood pressure will

mon in the developing world. Second, the difference

ultimately lead to long-term cardiovascular effects

in postpartum weight loss commonly reported in the

because hypertension studies have had short follow—

literature with lactation may be clinically insignificant.

up [70, 71]. Evidence for an association between lac-Finally, the associations of breastfeeding with child tation and CVD comes from the NHS, in which an

cognition and obesity also commonly cited in the lit—

inverse association between extended duration of lac—

erature may be largely confounded by factors related

tation and MI and sudden death was found in a large

to socioeconomic gradients, and it is unclear whether

prospective cohort with a long follow-up [69]. Further these relations can be attributed to residual or unmea-follow-up studies should examine the association in sured confounding.

large cohorts for sufficiently long durations to confirm

Although there is an extensive body of literature on

these results.

the potential benefits of breastfeeding, several areas

of research warrant further attention. First, the benefits of partial versus exclusive breastfeeding remain

Conclusions

unknown for many health outcomes. Second, combin—

On the basis of the epidemiological evidence, breast-ing both women who choose not to breastfeed and

feeding is a modifiable risk factor for several mater—

women who cannot lactate in a reference group of

nal and child health outcomes. Evidence suggests that

women who do not breastfeed may obscure important

breastfeeding may reduce the risk of lower respi—

differences. The inability to lactate may be associated

ratory and gastrointestinal infections in infants and

with metabolic and structural characteristics linked

TIIDM later in life. Other data imply that breast-to disease processes; conversely, the use of medica—

feeding may reduce the risk of maternal breast can—

tion to suppress lactation may interfere with a coor—

cer, although only for extended durations of breast—

dinated apoptotic process. Finally, further research is

feeding. Reports from a limited number of studies also

warranted to identify ways to promote breastfeeding

suggest an important reduction in risk of maternal

as a public health intervention. Large-scale trials of

CVD and TIIDM with longer lifetime durations of lac—

breastfeeding promotion such as PROBIT may help

tation.

to establish the feasibility of such interventions, while

However, commonly held misconceptions about

evaluating their impact on maternal and child health

the benefits of breastfeeding persist. For example, any

outcomes.

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Section 3

Specialized requirements

Chapter

12 Teenage pregnancies

Annie S. Anderson and Wendy L. Wrieden

Key clinical messages

pregnancy vary enormously between the developed

and developing world and are influenced by cultural

Teenage pregnancy is associated with poorer fetal and

norms, kinship, and social support.

maternal outcomes including higher rates of low birth

Within Europe, the United Kingdom is often cited

weight infants (Ↄ 2500 g) and neonatal deaths.

as having the highest teenage conception rate. In 2003,

Nutritional requirements for pregnancy must meet

the rate was 42.3 per 1000 in England and Wales

the maternal and fetal needs of pregnancy plus

[1], but this is substantially lower than New Zealand the requirements for personal growth in the young or the United States [2], and in fact overall interna-
mother.

tional comparisons suggest that the rate is moder—

Adolescent pregnancy growth is associated with

ate and has declined over the past 60 years. Lawlor

greater weight gain, fat storage, and postpartum weight

and Shaw [2] noted that “over the same three to retention compared with older women but also a six decades the number of adolescents having sex

greater incidence of low birth weight babies.

has increased greatly (Wellings & Kane, 1999)[3] and In adolescence, high pre-pregnancy body mass the age at menarche has decreased (Whincup et al.,

index (BMI) and high weight gain during preg—

2001)” [4]. Thus, although the at-risk population has nancy independently confer dose-dependent increases increased overall, declining conception rates indicate

in risk for macrosomia, primary cesarean deliv—

that teenagers must in fact be fairly competent at pre—

ery, labor induction, pregnancy-induced hyperten—

venting unwanted pregnancies.

sion, preeclampsia, and gestational diabetes mellitus.

In the United States, approximately 900,000

For younger adolescents, higher gestational weight

teenagers become pregnant each year, and even with

gains are recommended, but this should be assessed on

declining rates, it is estimated that more than 4 in

an individual basis according to pre-pregnancy weight.

10 adolescent girls have been pregnant at least once

Where possible, pregnant teenage women should

before age 20 years. It should also be noted that

be given individual counseling that focuses on moti—

approximately 25% of adolescent births are not first

vation and skills for changing eating habits to help

births [5]. Preliminary data for 2005 [6] show that the achieve appropriate dietary intake. Such counseling birth rate for teenagers declined by 2% in 2005, falling

must take account of individual social and economic

to 40.4 births per 1000 for those aged 15 to 19 years

circumstances.

(the lowest ever recorded in the 65 years). The rate

Access to financial support with food aid and

declined for teenagers 15 to 17 years to 21.4 births per

practical advice appears to be a rational approach to

1000, but was essentially stable for older teenagers 18

help achieve dietary change, but the impact of such

to 19 years, at 69.9 per 1000 [6]. By contrast, in Brazil, approaches on uptake and outcomes remains to be the birth rate for adolescent mothers has increased

tested.

from 8.0 per 1000 in 1980 to 9.1 per 1000 in 2000, now

representing 19.4% of all births (cited by Gigante *et al.*

Introduction

[7]).

Teenage pregnancy presents biological, social, and cul—

Teenage mothers are less likely to attain high levels

tural challenges to young women as they strive to cope

of education, work experience, and financial stability.

with the physiological and emotional demands of ado—

U.S. data suggest that as many as 83% of adolescents

lescent issues, fetal growth, and impending mother—

who give birth and 61% of those who have had abor-

hood. At a global level, the nutritional issues of teenage

tions are from poor or low-income families and that

Section 3: Specialized requirements

Table 12.1 Live births, stillbirths, and infant deaths by mother’s age 2006

England and Wales

Number and rates

Number of births

Ratesa

Mother’s age

Live births

Stillbirths

Stillbirth

Perinatal

Neonatal

Postnatal

Infant

All

669,514

3,603

5.4

7.9

3.4

1.4

4.8

Under 20

45,500

268

5.9

8.8

4.1

2.3

6.4

20–24

127,814

682

5.3

8.0

3.6

1.9

5.6

25–29

172,642

887

5.1

7.8

3.6

1.2

4.8

30–34

189,369

920

4.8

7.2

3.0

1.1

4.1

35–39

110,473

640

5.8

8.0

3.1

1.3

4.3

40 and over

23,716

206

8.6

12.0

4.4

1.4

5.9

Source: Office for National Statistics, Infant and perinatal mortality by biological and social factors 2006. Health Stat Q (2007), 36:84–91.

a Stillbirths and perinatal deaths per 1000 live births and stillbirths. Neonatal, postnatal, and infant deaths per 1000 live births.

at least one third of parenting adolescents are the chil—

ing perinatal asphyxia, jaundice, and respiratory dis—

dren of adolescent parents.

tress syndrome). Teenage pregnancy was also associated with higher fetal and neonatal mortality.

A range of biological factors has been associated

Medical risks of teenage pregnancy

with these unfortunate pregnancy outcomes, includ—

There is considerable evidence worldwide that teenage

ing poor nutritional status, low pre-pregnancy weight,

pregnancy is associated with increased maternal and

maternal height, parity, and poor weight gain during

fetal risk. For example, in the United States, the inci—

pregnancy. These factors in turn are highly likely to

dence of having a low birth weight (LBW) infant

have been influenced by social circumstances includ-

(Ↄ 2500 g) among adolescents is more than double

ing poverty, poor social support, low educational lev—
the rate for adults, and the neonatal death rate (within
els, substance abuse (smoking and drugs), and poor
28 days of birth) is estimated to be almost 3 times
uptake of antenatal services.
higher. The mortality rate for the mother, although
low, is twice that for the adult pregnant woman [8].
In England and Wales, women under 20 years have a
Nutritional requirements of
greater risk of stillbirth, perinatal, neonatal, postnatal,
and infant death compared with mothers aged 21 to 40
adolescent pregnancy
years (Table 12.1).
Key characteristics of dietary habits in adolescence in
However, the incidence of teenage pregnancy and
developed countries have been described as unconven—
the impact on health may be most visible in the
tional meal patterns (particularly snacking), chang—
developing world. In a community-based, multicen—
ing food consumption and choices (including a domi—
ter study of 93 356 married women, aged 15 to 45

nance of savory snacks, confectionery, and sweetened

years, from 23 districts in India, Oumachigui [9]

beverages), and concerns with body weight. It is rec—

reported that 40% to 80% of women married before

ognized that many of these features reflect the need to

age 18 years, and the incidence of teenage preg—

express freedom from parental control and from adult

nancy was 66%. More recent research from a ter—

tastes and lifestyles [11]. Adolescence is also a time tiary care teaching hospital in Varasi, India [10],

where many experiment with tobacco, alcohol (often

reported that compared with adult controls, there were

to excess), and other substances. It is also recognized

increased complications of teenage pregnancy includ—

that levels of psychological distress have increased

ing pregnancy-induced hypertension, preeclamptic

among female adolescents in recent years because of

toxemia, eclampsia, and premature onset of labor.

increasing educational expectations and issues over

Teenage mothers also had increased incidence of LBW,

personal identity [12], which may result in suboptimal **120**

premature delivery, and neonatal morbidities (includ—

health behavior choices. Additionally, peer influence

Chapter 12: Teenage pregnancies

Table 12.2 Nutrient intakes recommended for teenage and nonteenage women
Australian and New Zealand United States

Recommended Dietary Intakesa

Recommended Dietary Allowancesb, c 14–18 yr

19–30 yr

31–50 yr

≤18 yr

19–30 yr

31–50 yr

Energy (kcal)

Guidance given

Guidance given

Guidance given

2368, 2708,

2403, 2743,

2403, 2743,

according to

according to

according to

2820d

2855d

2855d

PAL and

PAL and

PAL and

weight

weight

weight

Protein (g/day)

58

60

60

71

71

71

Vitamin A (g/day)

700

800

800

750

770

770

Vitamin C (mg/day)

55

60

60

80

85

85

Folate (g/day)

600

600

600

600

600

600

Iron (mg/day)

27

27

27

220

220

220

Calcium (mg/day)

1300

1000

1000

AI 1300

AI 1000

AI 1000

Zinc (mg/day)

10

11

11

12

11

11

Chromium (mg/day)

AI 30

AI 30

AI 30

AI 29

AI 30

AI 30

a Source: Nutrient Reference Values for Australia and New Zealand: Including Recommended Dietary Intakes (Department of Health and Ageing, National Health and Medical Research Council, 2006).

b Source: Dietary Reference Intakes for Energy, Carbohydrate, Fiber, Fat, Fatty Acids, Cholesterol, Protein, and Amino Acids (Macronutrients), Food and Nutrition Board and Institute of Medicine (Washington, DC: National Academy Press, 2005).

c Source: Dietary Reference Intakes for Vitamin A, Vitamin K, Arsenic, Boron, Chromium, Copper, Iodine, Iron, Manganese, Molybdenum, Nickel, Silicon, Vanadium, and Zinc, Food and Nutrition Board and Institute of Medicine (Washington, DC: National Academy Press, 2000).

d PAL = physical activity levels. First, second, and third trimesters, respectively.

and peer group expectations contribute to a range of

increasing maternal tissue, fetal growth and devel—

food and drink choices.

opment, and additional energy costs associated with

In the United Kingdom, the most recent large scale

increasing metabolism) have been identified by a num—

survey of young women, the National Diet and Nutri—

ber of scientific bodies (e.g. the 1991 Department of

tion Survey (NDNS) of Young People aged 4 to 18

Health report [14]), but these do not always include years [13], reports that the dietary intake of teenage allowances for the teenage mother, who may still have girls is far from desirable. As an indication of fruit and

greater nutrient requirements for her own growth.

vegetable intake, during the 7-day recording period

For example, nutrient recommendations issued for

over which dietary intake was measured, 80% of 15—

the United States [15] and Australia [16] provide fig-to 18-year-old girls had not eaten any citrus fruits, and ures for pregnant women under 18, but these are

60% had not eaten any leafy green vegetables. Nonmilk

in the main similar or lower than those given for

extrinsic sugar intakes were also high, with as many as

older women except for calcium and phosphorus (see

83% of 11-to 14-year-old and 78% of 15-to 18-year-

Table 12.2). However, this simply reflects the increased old girls above the maximum recommended intake, requirement for these nutrients by this age group

the main source being carbonated soft drinks. In addi—

and/or body size rather than any special need iden—

tion, intakes of iron, calcium, and magnesium were

tified due to pregnancy per se. Special requirements

particularly low in teenage girls with, for example, 51%

may also be needed for women who are under-or over—

of 11-to 14-year-olds and 50% of 15-to 18-year-olds

weight. Thus, an exact, personalized energy regimen

consume less than the lower reference nutrient intake

may be difficult to estimate in clinical practice, and the

[14] for iron.

reassurance provided by measurements of fetal growth

Pregnancy is a period of rapid growth and develop—

are thus important.

ment of the fetus, with high physiological, metabolic,

Adequate nutrient intake during pregnancy is

and emotional demands on the mother. Nutrient

important to enable the fetus to grow and develop

requirements for pregnancy (to meet the needs of

physically and mentally to full potential and will also

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affect adult nutritional status of the mother. There is

Sukalich *et al.* [26] reported findings from a ret-evidence to show that growth in stature (as assessed by rospective case-control study of 1498 overweight sub—

knee height measures) continues after menarche and

jects (Ɔ 25 kg/m2) who were aged younger than 19

during teenage pregnancy. This growth is associated

years. This population-based study demonstrated that

with increased weight gain, fat storage, and greater

overweight adolescent women are at increased risk

postpartum weight retention [17]. Howie *et al.* [18]

for a number of adverse perinatal and neonatal out—

reported that 27% of adolescent mothers gained exces—

comes (which were independent of the presence of gessive weight (more than 40 pounds [18.4 kg]) during

tational diabetes mellitus or gestational weight gain).

pregnancy compared with 18% of older women. A

These outcomes included primary cesarean deliv—

recent article from Brazil [7] has also reported that ery, labor induction, pregnancy-induced hyperten-BMI of teenage mothers was 0.81 kg/m2 higher than sion, preeclampsia, and gestational diabetes mellitus. It

teenagers who had not become pregnant and was 1.58

is notable that an increased incidence of macrosomia

kg/m2 higher in those who had two teenage preg—

and a decreased incidence of LBW infants and small—

nancies. Despite this weight gain, adolescent mothers

for-gestational-age infants were reported. Increasingly,

tend to give birth to infants with lower birth weights

pre-pregnancy BMI and weight gain during pregnancy

(by 150–200 g) than those of infants born to older

independently confer dose-dependent increases for

women [19–21]. It has also been shown that growing these risks.

adolescents have a surge in maternal leptin concen—

The authors concluded that “obese women are at

trations during the last trimester, which may reduce

increased risk for adverse perinatal and neonatal out—

the rate of maternal fat breakdown during late preg—

comes and that youth does not ameliorate this effect.”

nancy and thereby increase the mother’s use of glu—

With rates of overweight increasing at all ages and ado—

cose for energy. This diminishes energy supply for fetal

lescent pregnancy a continuing problem, overweight

growth, accounting for higher maternal fat gains and

in the gravid adolescent is a pressing perinatal public

lower birth weights among growing teenage pregnant

health concern.

women [22]. In recognition of the energy needs of For the overweight or obese adolescent mother, the growing mother and growing baby, a higher ges—

appropriate weight gain recommendations are an

tational weight gain is recommended for young girls

important part of relevant counseling during preg-

(especially if they are less than 2 years postmenarche)

nancy. Postpartum weight loss also becomes extremely

in the United States [23, 24] in an attempt to facilitate desirable in relation to her own well-being, to meet the energy requirements.

physical demands of parenting, to reduce the risk of

An increasingly recognized concern for pregnant

obesity-related complications (hypertension, glucose

adolescence is high BMI. Groth [25] discussed cat-intolerance, and congenital malformations) in further egorization of BMI by Institute of Medicine (IOM)

pregnancies [27], and to promote future family health.

cutoffs used in recommendations for weight gain dur—

It is, however, recognized that not all pregnant ado—

ing pregnancy and the Centers for Disease Control and

lescent women gain high amounts of weight during

Prevention (CDC) BMI percentiles for classifying ado—

pregnancy. Scholl *et al.* [28] demonstrated that adolescent body size in 347 primiparous black adolescents.

lescents with inadequate weight gain produced babies

Using CDC centiles for adolescents, 24% of the sam—

with a lower birth weight (180 g) and an increased

ple were classified as at risk for overweight (≥ 85th

prevalence of LBW overall. After adjusting for poten—

percentile and Ↄ 95th) or overweight (≥ 95th per—
tial confounding variables, teenagers who went on
centile) compared with 19% using IOM cutoff points.
to develop inadequate total weight gain for gestation
These observations are a sharp reminder of the inci—
had consumed 1878 kcal daily, versus 2232 kcal for
dence of excess body weight in vulnerable adolescents
teenagers with adequate total gain (p Ↄ 0.05). They
but also a reminder that the IOM categories tend to
also had significantly lower protein and carbohydrate
classify more of this group as underweight (28%) com—
intake. However, there was no direct effect of nutri—
pared with CDC categories (2%) and therefore they
ent intake on birth weight, LBW, or preterm delivery.
may be receiving inappropriate guidance for gesta—
These findings suggest that the relationship between
tional weight gain, contributing to excess final weight
nutrient intake during pregnancy and birth weight
and increased risk for overweight in the postpartum
may be indirect and moderated by weight gain during

period.

pregnancy.

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Micronutrient depletion and pregnancy

poor nutritional status at conception because of recent

outcome

maternal growth and/or inadequate food supply may

benefit from receiving food and micronutrient supple—

Poor maternal micronutrient status also is likely to

ments during pregnancy and in the postpartum period

influence pregnancy outcome. Poor maternal iron,

to improve overall nutritional status for adult health

zinc, and folate status has been associated with preterm

and future pregnancies.

births and intrauterine growth retardation, two outcomes for which teenage women are likely to be at high

Interventions to improve nutritional

risk. A poor maternal folic acid status at conception

may contribute to the poor reproductive outcomes in

intake of teenage pregnant women

women. In young mothers, it is likely that other health

The nutritional needs of pregnant adolescents are the

behaviors (e.g. smoking and alcohol) will also affect
greatest at a time when it is often socially and cultur—
folate status, and use of folic acid supplements is also
ally most difficult to achieve them. Dieting, skipping
likely to be less common. Data from the United States
meals, snacking, eating away from home, consuming
(http://www.cdc.gov/mmwr/preview/mmwrhtml/
fast foods, and trying unconventional diets are chal—
mm5701a3.htm) indicate that among all women of
lenges to achieving the nutrient dense diet required to
childbearing age, those aged 18 to 24 years had the
optimize growth and development in the mother and
least awareness regarding folic acid consumption
child. Because of poor dietary habits in the preconcep-
(61%), the least knowledge regarding when folic acid
tion period, many young women start pregnancy with
should be taken (6%), and the lowest reported daily
reduced nutrient stores and increased risk of nutri—
use of supplements containing folic acid (30%).
tional deficiencies. It is recognized that up to 50% of
Iron-deficiency anemia is a prevalent problem

all pregnancies are likely to be unplanned [31], and among pregnant adolescents and is associated with this is likely to be higher among adolescent women.

preterm delivery and associated LBW. It is hypothe—

Thus, although nutritional interventions for women

sized that the excess preterm birth rate among teenage

are likely to have the greatest effect if delivered before

women may be related to poor maternal iron stores

conception and during the first 12 weeks, the practi—

resulting from recent growth demands [29].

calities of achieving this goal are substantially reduced

The circulating concentrations of other nutrients,

in younger women.

such as zinc, vitamin A, vitamin B6, and vitamin B12,

Attempts to change dietary habits must move well

also decline during pregnancy, but the concentrations

beyond the provision of standard nutrition education

of those nutrients return to normal shortly after deliv—

and use culturally sensitive counseling strategies that

ery, suggesting that they are less likely to be low in

take account of increased independence, busy sched—

pregnant adolescents [22], although this is a topic of ules, search for self-identity, peer influence, group concurrent investigation. For example, Maia *et al.* [30]

formity, and body image dissatisfaction. Pregnancy

reported that zinc and copper biochemical responses

has often been viewed as a time to promote dietary

to pregnancy in adolescent women appeared quali—

change [32]; however, Callins [33] wisely remarks that tatively similar to those described in adult women, “although behaviour change in any age group presents

although they suggest that a poor maternal zinc status

a formidable challenge, it has the greatest potential for

may limit the metabolic adaptation capacity of adoles—

improving obstetric and neonatal outcomes in preg—

cent women during pregnancy.

nant adolescents.” She goes on to call for counseling

Adolescent pregnancy is associated with increased

support for overweight and obese adolescents before,

risk for preterm birth and growth-restricted infants.

during, and after pregnancy, making the important

Maternal nutrient depletion has been proposed as

recommendation that psychological, environmental,

a possible cause of these poor pregnancy outcomes

socioeconomic, and educational factors should be

[22]. Low intake of food (total energy) is likely to incorporated into behavior

change strategies. It is clear affect the intake of all nutrients and have a signifi—

that there are unique opportunities for obstetricians to

cant impact on maternal nutritional status at concep—

work in a “team organized, patient focused approach to

tion, which in turn has the potential to influence preg—

decrease the adverse outcomes in subsequent pregnan—

nancy outcomes. Thus, it seems reasonable to surmise

cies and decrease long term risk of chronic diseases.”

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that individuals who are demonstrated to be at risk of

Hunt *et al.* [34] have commented that the nutritional **Section 3: Specialized requirements** component of standard prenatal care will not be suffi—

rots, milk, cheese, eggs, and tuna. Participants receive

cient to support positive dietary changes among preg—

food prescription vouchers, which can be exchanged

nant adolescents and that it is likely that this popula—

at authorized WIC retailers in exchange for the foods

tion subgroup will require repeated exposure to both

specified on the voucher.

information and strategies that build motivation as

The choice of foods that vouchers can be used for

well as skills for changing eating habits [35].

reflects nutrient needs, although it should be noted

Ideally, all pregnant teenagers should have their

that there may be increasing interest in promoting

dietary habits assessed and should be offered per—

milk given recent findings that high milk consump—

sonal dietary counseling, which may include vitamin

tion is associated with lower incidence of LBW babies

and mineral supplements if nutritional intake is below

across the general maternal population [37]. It is standard (or if appropriate nutritional status markers speculated that this may relate to water-soluble sub—

for pregnancy indicate primary deficiency). In addi—

stances in milk that increase fetal growth (e.g. through

tion, the weight-gain pattern should be monitored to

increasing blood concentrations of insulin-like growth

ensure that energy intakes are sufficient to support a

factor 1).

gain of about 0.4 kg (1 lb) per week in the second and

Nutrition education regulations define two main

third trimesters.

objectives – namely, to stress the relationship between

Interventions to improve dietary changes can act proper nutrition and good health and to assist individ— by affecting modifiable factors at an individual level, uals at nutritional risk in achieving a positive change in such as dietary knowledge, beliefs, and attitudes, and food habits resulting in improved nutritional status. improving psychosocial components, such as self— In 2002, 11% of participants of WIC were preg— efficacy. However, the long-term effect of these will nant women. Although there are few data available on ultimately be enhanced and facilitated by societal the impact of WIC participation on adolescent preg— interventions that tackle the context and situation of nancy outcomes, participation in the program pro— the living environment and the balance between health vides strong suggestive evidence that WIC has a pos— promotion and food industry marketing. Successful itive impact on mean birth weight, the incidence of health promotion campaigns such as those designed to LBW, and several other birth outcomes. Although the improve folic acid uptake in the preconception period

inherent research errors of self-selection make it dif—

are known to be less effective in younger women

ficult to translate fully the available data, analysis has

[31]. Dietary interventions cannot tackle unmodi-shown that the positive effects of the program can lead fiable demographic characteristics such as socio—

to savings in Medicaid [38], although the magnitude of economic status of women, but available income effect has been questioned [39].

will both influence and be influenced by dietary

Another U.S. program that has demonstrated the

interventions [36].

achievement of changes in dietary awareness and

The improvement of nutrition and health is a

empowering participants to change dietary practices

major aim of the U.S. Special Supplemental Food

is the Expanded Food and Nutrition Education Pro—

Program for Women, Infants and Children (WIC),

gram (EFNEP; http://www.csrees.usda.gov/nea/food/

which provides federal grants to states for supplemen—

efnep/about. html) [40]. This program, which has been tal foods, health care referrals, and nutrition education running for many years, is a federally funded nutri—

for low-income pregnant, breastfeeding, and non—

tion program aimed at assisting low-income youth and

breastfeeding postpartum women and to infants and families (with young children) and ethnic minorities to children up to age 5 who are found to be at nutritional acquire practical food knowledge, skills, attitudes, and risk (http://www.fns.usda.gov/wic). Although not spe— behavior change (including money management and cific to teenage women, the program is likely to have getting the most from health assistance programs) to benefits for this group if they participate. The pro— help achieve nutritionally sound diets. As with WIC, gram has traditionally centered around five nutrients it is not specific to teenage women (although some (protein, calcium, vitamin A, vitamin C, and iron). programs have been designed specifically for this tar— WIC funds are divided between supplemental foods get group) but is again likely to be useful for this (75% of funds) and nutrition education (one sixth of vulnerable group overall. The program focuses on an the administration funds) with food vouchers pro— experiential learning process; adult program partic-

vided during pregnancy for cereal, juice, legumes, car—

ipants learn how to make food choices to improve

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the nutritional quality of the meals they serve their

counseling alone or with two types of food supple—

families, and the youth program may also tackle wider

ment given during second and third trimesters had

health behaviors. Participants gain or enhance new

significantly greater mean birth weight compared with

skills in food production, preparation, storage, safety,

women in the control population

and budgeting. EFNEP is delivered as a series of 10 to

Little work has been undertaken on interven—

12 or more lessons, often over several months, by para—

tions aimed at improving access to healthy diets, food

professionals and volunteers and may include individ—

affordability and availability, and practical issues such

ually tailored home-education sessions [41]. The proas food skills in adolescent women. One published gram has been shown to influence a range of food

study from University of Dundee evaluated the fea—

practices (including food budgeting, food safety, and

sibility of a cooking skills program led by midwives

food preparation) [42]. A number of EFNEP intervenin a community setting for teenage pregnant women.

tions have targeted pregnant adolescents with encour—

The program [46] incorporated seven informal food-aging results on nutritional status, including weight preparation sessions and opportunities for discussion

gain during pregnancy [34].

of food and health matters (including food safety

In a review of interventions to improve diet and

and well-being in pregnancy). Although the midwives

weight gain among pregnant adolescents undertaken

found the package easy to follow and use, only 16 (of

to identify promising strategies for effective interven—

the 120 invited) women attended the course, and the

tions, Nielson *et al.* [43] critically reviewed 27 arti-authors concluded that alternative methods of deliver-cles including 13 controlled trials that specifically tar—

ing and evaluating such a package should be investi—

geted pregnant adolescents and six that included this

gated.

subgroup within the study population. Most exam—

Following a revision of the Welfare Foods scheme

ined birth weight and gestational weight gain, but

in the United Kingdom, a new food-based nutri—

none were concerned with risks of excessive weight

tion intervention scheme (“Starting Well”) is currently

gain. Positive outcomes were thought to be due to

rolling out from the Department of Health across

multidisciplinary team approaches supporting psy—

the United Kingdom for teenage pregnant women

chosocial needs, individualized counseling, home vis-

(Ↄ 18 years), low-income pregnant women, and young

its (and outreach to highest-risk teens), visual presen—

families [47]. During pregnancy, eligible women will tations and tracking of gestational weight gain, and receive vouchers for £2.80 per week, which can be

support group work. In addition, the authors noted

used for milk, fresh fruits, and vegetables, and free

that only one study examined employed a theoretical

supplements containing vitamin C, vitamin D, and

framework, and they hypothesize that greater effects

folic acid; advice will be available in relation to prac—

could be achieved by the application of behavior—

tical aspects of healthy eating. Although the scheme

change strategies that have been successfully uti—

has some similarities to the U.S. programs described

lized in wider population-based dietary intervention

earlier, the total monetary value of vouchers is con—

studies.

siderably less, and the advice program has yet to be

In the United Kingdom, there has been a long his—

described in systematic detail. It is also important to

tory of providing dietary advice during pregnancy, but

note that current policy work lacks robust evidence

the impact of this has rarely been rigorously assessed.

that such initiatives are likely to have a significant

Anderson *et al.* [44] undertook a minimal contact effect on dietary intakes during pregnancy and subse-nutrition education intervention program and demon-quent maternal and fetal health outcomes. The scheme strated that nutrition knowledge can be increased

should now be evaluated for such outcomes. There

through education programs, but this has little impact

is considerable skepticism about the small monetary

on dietary behaviors. More intensive dietary counsel—

value of the food vouchers [31]. In addition, an analysis ing for pregnant women indicates that nutrient intake of how successful such initiatives might be in an envi—

can be improved during pregnancy, but there is no

ronment that promotes excess consumption has not

consistent evidence that nutrition counseling has an

been undertaken, and this might be particularly rel—

impact on rates of LBW, gestational age, or length of

evant with respect to weight gain in overweight preg—

birth. However, Doyle *et al.* [45], in a nonrandom-nant teenage women. Clearly, this scheme needs care-ized trial in London, demonstrated that intervention ful evaluation and monitoring of process, impact, and

women who received multiple episodes of nutrition

outcomes.

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A window on the realities of dietary intake, food

mote healthy food choices during pregnancy, but fur—

choices, poverty, and life for the pregnant teenager is

ther research is necessary to produce an evidence base

provided in a recent report by the Maternity Alliance

to inform program development and to ensure that

[48], highlighting the day-to-day problems of trying to the most vulnerable infants and women in society are attain a modest but adequate diet on a limited bud—

given the best possible nutritional reserves for future

get. Clearly much work is being undertaken to pro—

health [49].

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16:65–6.

Chapter

13**Vegetariansandvegansduringpregnancy**

and lactation

Rana Conway and Adrienne Cullum

Introduction

viving on a largely (if not exclusively) vegetarian diet

may be high due to poverty and economic reasons. In

A number of studies have been used to assess the ade—

India, 20% to 30% of the total population are thought

quacy of consuming a vegetarian diet during preg—

to be vegetarian for religious reasons, but substantial

nancy. A small number of studies have compared preg—

additional numbers may seldom eat meat because of

nancy outcomes for different types of vegetarians with

economic reasons. In developed countries, such as the

those of nonvegetarians. A limited amount of data have

United States and United Kingdom, between 2% and

also been gathered on the nutrient intakes of vegetar—

7% of the population are vegetarian, the figures vary—

ians during pregnancy. However, there is little good

ing depending on who sponsors and collects the data

evidence regarding nutrient status (e.g. hemoglobin or

and how dietary intakes are assessed. A significant

serum vitamin B12 levels) during pregnancy or lacta—

amount of the population may not classify themselves

tion, therefore studies of nonpregnant vegetarians are

as vegetarian but eat fish but not meat, eat meat rarely,

useful.

or avoid red meat but not other types of meat [2]. For Figure 13.1 summarizes the main categories of veg-example, the U.K. Food Standards Agency Consumer etarian diets. Being vegetarian while pregnant or lac—

Attitudes Survey 2007 [3] found that 7% of all respon-tating cannot be assumed to be risky. For example, dents (i.e. all age groups and both sexes combined)

women may benefit from higher intakes of fruit and

claimed to follow a vegetarian diet, and a further 5%

vegetables and whole grain, and lifestyles associated

claimed to be “partly vegetarian.”

with a vegetarian diet: they may be more active, less

In developed countries, more women than men

likely to smoke or binge drink, and less likely to be

tend to be vegetarian, and vegetarians tend to be of

obese or have diabetes [1]. The balance of benefits and higher educational or socioeconomic status, less likely risks of a vegetarian pregnancy is likely to depend on

to have children, and more likely to be under 40

how restrictive the diet is. The reasons for following

years of age [2]. There are also likely to be differences a vegetarian diet may also play a part; in developed between ethnic groups. In the United Kingdom, people

countries people choose to be vegetarian or vegan for

of nonwhite ethnic origin are more likely to describe

a variety of reasons including health, ethical concerns,

themselves as vegetarian than white respondents (15%

and religious beliefs. Risks associated with vegetar—

vs. 6% of white respondents) [3].

ian diets are more likely for those on more restrictive

Because of the substantial differences in preva—

regimes – both those following a more extreme vegan

lence between countries, the available evidence, and

diet and those following a lacto-ovo (LOV) vegetar—

the differences in specific dietary recommendations

ian diet, but on a restrictive choice of foods. In addi—

between countries, this chapter focuses primarily

tion, the diets of affluent vegetarians in Europe or the

on evidence, guidance, and recommendations from

United States are likely to be very different in quality

developed countries, particularly the United King—

from those of deprived vegetarians in South Asia.

dom.

The prevalence of women of childbearing age following a vegetarian diet is likely to vary substantially between developed and developing countries.

Clinical approach

Although in some countries, such as Brazil and China,

There is no national, evidence-based, clinical guidance

the total numbers of vegetarians are thought to be neg—

on vegetarian pregnancy or lactation. In England, the

ligible, the worldwide population of individuals sur—

National Institute for Health and Clinical Excellence

r

Muslim nonvegetarians or European nonvegetarians

Lacto-ovo vegetarians (LOVs) avoid meat, poultry

[8, 9]. However, although differences between Hindus and fish but consume milk, dairy and eggs.

r

and Europeans remain significant after adjustment for

Vegans consume no food of animal origin.

r

length of gestation, sex of infant, maternal height and

Macrobiotics consume whole-grain cereals,

especially brown rice, plus vegetables, beans, sea

weight, and parity, those between Hindus and Mus—

vegetables, and miso soup. Other foods including

lims do not. The effect of vegetarianism alone cannot

fruit and fish are eaten occasionally, and dairy and

be concluded from these studies because pregnancy

eggs are avoided.

outcome may have been affected by genetic differences

r Individuals describing themselves as

between the ethnic groups. A more recent study com—

semivegetarian may restrict their intake of red

paring Caucasian LOV, fish eaters, and nonvegetarians

meat, poultry and/or fish.

found no significant differences in birth weight, length

of gestation, birth length, or head circumference [10].

Figure 13.1 Categories of vegetarian diets.

Smaller studies in the United States similarly found

no differences between the birth weights of LOVs and

nonvegetarians.

(NICE) has issued guidance on maternal and child

A tendency toward lower birth weights has been

nutrition [4], postnatal care [5], and antenatal care [6];

reported among vegans in the United Kingdom [11].

although these do not specifically address vegetarian

However, this was not found to be the case among

pregnancy, the recommendations apply in general. The

members of a vegan commune in Tennessee, where

Dietary Guidelines for Americans 2005 briefly men—

pregnant women routinely received multivitamin and

tion how the population guidelines can be adapted to

mineral supplements and advice about increasing proa vegetarian diet [7].

tein intake [12]. Studies of women following a macro-Because there is no specific dietary guidance for biotic diet in the United States and the Netherlands

vegetarian women during pregnancy and lactation,

have reported lower birth weights [13, 14]. In both standard dietary advice – such as guidance on precon-countries it was found that women following the most ceptual intake of folic acid, avoidance of alcohol, avoid—

restrictive macrobiotic diets, for example, those eating

ance of certain foods to prevent risk of food poison—

dairy foods and fish less than once per week, were more

ing (such as soft cheese), and intake of sufficient fiber

likely to have smaller babies. These studies highlight

and water to prevent constipation (as that issued by, for

that although women following very restrictive veg-example, the Department of Health, Food Standards

etarian diets are nutritionally vulnerable, even those

Agency, and National Institute for Health and Clinion vegan or macrobiotic diets can be reassured that

cal Excellence in England and the Centers for Disease

it is possible to have a good nutrient intake while still

Control and Prevention in the United States) – will

adhering to their dietary principles.

need to be adapted.

Those studying pregnant vegetarians have specu—

Both health professionals and women themselves

lated that lower birth weights (where observed) may be

are likely to have concerns about following a vege—

related to lower energy or protein intake or inadequate

tarian diet during pregnancy or lactation. However,

iron, zinc, vitamin B

the issues they rate as important may differ substan—

12, or essential fatty acid status.

tially. Although a vegetarian diet is often associated

with a healthier lifestyle, health professionals should

Energy and macronutrients

not assume that vegetarian pregnant women have bet—

Vegetarians, on average, have a lower body mass index

ter (or worse) diets than average or are necessarily fol-

(BMI, kg/m2) than nonvegetarians [15]. This is prob-lowing standard dietary (and other) advice for preg-ably because of the higher fiber content and lower nancy and lactation.

energy density of vegetarian diets. Indeed, it has also

Health professional concerns

been speculated that some young women may adopt

a vegetarian diet as a means of weight reduction or

control. Although this is not an issue for the average

Pregnancy outcome

vegetarian, it should be considered for some severely

In the United Kingdom, lower birth weights have

underweight vegetarians or vegetarian women who

been reported among Hindu vegetarians than either

are gaining little weight during pregnancy, and

 handled appropriately. Because vegetarian diets, and Table 13.1 Nutrients that may be of concern in vegetarian

vegan diets in particular, can be bulky it may be

diets and good food sources for different types of vegetarians

appropriate to encourage more energy-dense, but also

Nutrient

LOVs

All vegetarians

nutrient-rich foods such as avocados, nuts and seeds,

dried fruit, and fortified breakfast cereals.

Protein

Milk, cheese,

Beans, peas, lentils, soy milk,

The protein intake of vegetarians is usually lower

yogurt, eggs

tofu, nuts, and nut butters

than that of nonvegetarians [15] but adequate for preg-Iron Eggs

Fortified breakfast cereals,

dried fruit such as apricots

nancy [10, 16]. LOVs can meet many of their pro-and raisins, whole-grain tein requirements through dairy produce. However,

cereals including bread, brazil

by eating a more varied diet with foods such as beans

nuts, almonds, broccoli and

peas, beans, and lentils

and lentils as well, their intake of iron, fiber, and B

vitamins will also be increased. Vegans tend to have

Calcium

Milk, yogurt,

Green vegetables including

cheese

cabbage and broccoli, and

lower protein intakes than LOVs and need to con—

fortified soy products

sume a variety of protein sources to meet their essential

Zinc

Hard cheeses

Whole grains, nuts, seeds,

amino acid requirements. Eating cereal foods (such as

legumes, and soy products

bread, rice, and pasta) as well as peas, beans, and lentils

Vitamin

Milk, yogurt,

Fortified soy products and

should be encouraged.

B12

cheese, eggs

yeast extract (e.g. Marmite).

Vegetarians usually have a higher carbohydrate

Vitamin D

Egg yolk

Fortified margarines, soy

intake than nonvegetarians, and they tend to consume

milks, and breakfast cereals

more unrefined carbohydrates and have a higher fiber

Iodine

Dairy products

Seaweed (small amounts),

intake as well [10, 15, 17]. Although high fiber intakes iodized salt, and fortified soy milk

are an advantage as far as pregnancy-associated constipation is concerned, very high intakes can reduce

LOV = lacto-ovo vegetarians.

absorption of essential minerals such as iron and zinc.

The addition of bran to meals is not recommended,

noting that some multivitamin and mineral supple—

and consumption of unrefined cereal products occa—

ments for pregnancy contain low doses of iron that

sionally may be advantageous.

will help women meet their daily requirements. If supplemental iron is required, some women may prefer

Iron

to take a natural iron supplement, such as Spatone

(http://www.spatone.com), which appears to be better

An increased risk of iron-deficiency anemia is a com—

absorbed than ferrous sulphate and causes fewer gas—

mon concern in relation to pregnant vegetarians. Stud—

trointestinal symptoms [20]. Advice regarding intake ies of nonpregnant women have generally found sim-of dietary iron may benefit all vegetarians. There are

ilar iron intakes among LOVs as nonvegetarians [15],

many good vegetarian sources of iron (Table 13.1), and and this is also true in pregnancy [10]. Studies of veg-iron absorption can be increased considerably by con-ans have found they usually have higher intakes of suming these with a good source of vitamin C, which

iron than nonvegetarians. However, this iron is non—

can be found in many fruits, fruit juices, and veg—

hem iron, which is less easily absorbed than hem iron

etables. In addition, tea should not be taken an hour

derived from meat. Studies of iron status have consis—

before or after a meal because it contains iron-binding

tently shown LOVs to have lower serum ferritin levels

polyphenols, which inhibit absorption.

than nonvegetarians [15, 17, 18], and they appear to be more likely to be diagnosed with anemia during pregnancy [10].

Folate

Despite these findings and anecdotal evidence of

LOVs generally have higher folate intakes than non—

anemia among vegetarians, routine iron supplemen—

vegetarians. Pregnant LOVs in Germany have been

tation is not advisable, because there is some evi—

found to have higher serum and red cell folate condence that in nonanemic women it may be detrimental

centrations than women following an average West-

[19]. Instead, vegetarians, like other pregnant women, ern diet [21]. Although vegetarian women of child-should be prescribed iron supplements only if blood bearing age are at lower risk of folate deficiency, they

tests demonstrate a need for them. However, it is worth

should still be strongly encouraged to follow standard

Section 3: Specialized requirements

advice to take a daily supplement of folic acid from

methylmalonic aciduria (an indicator of vitamin B12

preconception until the 12th week of pregnancy to

deficiency) has also been found among breastfeeding

reduce the risk of neural tube defects [4].

vegetarian women and their infants [27].

Vitamin B12 is required for the uptake of folate

Vitamin D

by cells, and vitamin B12 deficiency is considered an

independent risk factor for neural tube defects [28]. In The dietary sources of vitamin D are limited (they pregnant LOVs, red blood cell folate levels have been

are predominantly of animal origin and include oily

shown to be positively correlated with serum B

fish, fortified margarines, and some fortified breakfast

12 concentrations, suggesting that inadequate vitamin B

cereals, smaller amounts are found in red meat and

12 is

limiting the efficiency of folate utilization for some

egg yolk), and the main source is the synthesis fol-

[21]. If vegetarians have a good intake of dairy prod-lowing exposure of the skin to sunlight [22]. There is ucts and eggs, they should get enough vitamin B

long-standing advice in the United Kingdom (recently

12.

However, vegans need to consume fortified foods daily

reiterated by Scientific Advisory Committee on Nutri—

or take a supplement. Certain fermented soy products

tion [22] and NICE [4]) that all pregnant and breast-

(e.g. tempeh and miso) and marine vegetables are con—

feeding women should consider taking a daily sup—

sidered by some to be good sources of vitamin B

plement of vitamin D (10 g) to ensure their own

12.

However, up to 90% of the levels measured in these

requirement is met and to build adequate fetal stores.

foods may be inactive analogues [29].

However, uptake of vitamin D supplementation in

the United Kingdom is low, and vitamin D deficiency

Calcium

has reemerged as a public health concern, particularly for women and children from South Asian and

The calcium intake of vegetarians depends largely on

Afro-Caribbean groups [4]. Concern about maternal their intake of dairy products. LOVs tend to have sim-and infant vitamin D deficiency has also been raised ilar calcium intakes to nonvegetarians, but vegans usu—

in other countries in recent years, including Australia

ally have substantially lower intakes [15, 17, 18]. A [23] and the United States [24].

German study of vegan women recently found calIt has been suggested that low meat intake or a veg—

cium intakes to be 81% of recommended levels [30].

etarian diet may increase risk of rickets or osteoma—

A study of women following a macrobiotic diet in

lacia. However, it remains unclear whether observed

the United States found calcium intakes were approxi—

associations are due to dietary, religious, or cultural

mately half those of nonvegetarians during pregnancy

practices because studies have focused on particular

[27]. Breast milk calcium levels were not reduced [27]

groups of Asian vegetarians [25]. All vegetarian and but the implications for the mother's bone health are vegan women, particularly those with a restrictive diet

unclear.

and who are at greatest risk of deficiency (are obese,

have limited skin exposure to sunlight, or are of South

Zinc

Asian, African, Caribbean, or Middle Eastern descent

LOVs have been found to have lower zinc intakes than

[4]), should be encouraged to follow advice to take nonvegetarians during pregnancy in some [10], but a vitamin D supplement during pregnancy and while not all [16, 31], studies. There is concern that a vege-breast-feeding.

tarian's higher intake of fiber and phytate may reduce

bioavailability, but LOVs have not been found to have

Vitamin B12

lower serum zinc levels [16, 21, 31].

Vitamin B12 is found naturally only in foods of animal origin, and consequently lower intakes are found

Iodine

among vegetarians, both nonpregnant and pregnant

Low iodine intakes and status have been reported

[10, 15, 26]. A study of pregnant women in the Nether-among vegans, because the main dietary sources of lands found that LOVs were at increased risk of vita —

iodine are meat, fish, and dairy products [32, 33].

min B12 deficiency. On the basis of serum vitamin

There is limited evidence regarding iodine status dur—

B12 levels and plasma total homocysteine levels, it was

ing pregnancy and lactation, but to ensure an adequate

found that 22% of LOVs were vitamin B

132

12 deficient

intake, vegans need to regularly include foods fortified

compared with 3% of nonvegetarians [26]. Elevated with iodine or take a supplement.

Chapter 13: Vegetarians and vegans during pregnancy and lactation Women's concerns

focused on ensuring that women continue to eat a

wide variety of foods, that any aversions or crav—

On top of the usual concerns that many women have

ings do not result in their diet becoming yet more

during pregnancy and lactation, vegetarian women

restricted, and that alternative foods are suggested as

may be concerned about the impact of standard advice

necessary.

– such as the advice on food safety and nut con—

Some vegetarian or vegan women may decide to

sumption – on their dietary choices. Some women
introduce meat or other animal products to their diet
may feel guilty about avoiding animal products during
for one reason or another during pregnancy or lac—
pregnancy, may be concerned whether their body can
tation. Again, advice should ensure that women con-
“cope,” and may have experienced pressure from their
tinue to eat a wide variety of foods.
family, friends, or health professionals to change their
dietary habits. As for many women, pregnancy and
lactation may also raise long-standing issues about,

Peanuts and other nuts

for example, their weight and body image. Although
The frequency and quantity of nut consumption are
there is no evidence-based guidance addressing these
higher in vegetarian (particularly vegan) populations
concerns, there is no shortage of advice for women
than nonvegetarian populations [38]. Vegetarian online – entering “vegetarian pregnancy” into the pregnant and lactating women may be concerned
Google Internet search engine resulted in 18 700 hits
about how the impact of standard advice on peanut

(as of May 2008). However, the quality and consistency

consumption may affect the quality of their diets. In

of advice are highly variable. Providing women with

the United Kingdom, the Food Standards Agency

information about trusted, reliable sources of informa—

recommends that women who have a family history of

tion on diet and nutrition – such as the U.S. Depart—

allergic diseases (asthma, eczema, food allergies, etc.)

ment of Agriculture and the Food Standards Agencies

avoid eating peanuts during pregnancy and breast-in the United Kingdom and Australia – may be a use—

feeding and avoid introducing peanuts into the child's

ful first step. If women are looking for additional infor—

diet before 3 years of age. Committee on toxicity of

mation specific to vegetarians, they could be directed

chemicals in food, consumer products and the envi—

to the Vegetarian or Vegan Societies in the United

ronment (2008). Statement on the review of the 1998

Kingdom.

COT recommendations on peanut avoidance. http://

cot.food.gov.uk/pdfs/cotstatement200807peanut.pdf.

Cravings and aversions

Unlike the U.K. advice, the American Academy of

Although it is reported that meat is one of the foods

Pediatrics (AAP)[39] extends its advice to tree nuts that many women report developing an aversion to (such as almonds and cashews) for women who are

during pregnancy [34, 35], vegetarian women have breast-feeding. This would seem prudent, given that also reported craving meat [10]. Women may be con- between 30% and 50% of children with peanut allergy cerned that craving meat means their body is not able

(around 1.5% of children,) will have a sensitization

to "cope" without meat or that it signifies that they are or allergy to tree nuts [40]. There is currently some deficient in nutrients contained in meat such as iron, scientific uncertainty about whether young children

vitamin B12, or protein. Other common cravings or

should avoid peanuts to escape sensitization or instead aversions may include foods that make a significant

should eat peanuts to induce early oral tolerance and

contribution to the diets of vegetarian women includ—

thus prevent peanut allergy. However, although there

ing eggs (aversion [36]) and dairy products (craving are major studies under way to resolve this issue [41],

[36] or aversion [34]).

it is prudent for women to adhere to the existing

Women can be assured that there is little evi—

advice.

dence of a direct relationship between a food craving

The AAP [39] makes clear that its advice is based and nutrient deficiency [37]; other factors – such as on the fact that nuts are not an essential food and their changes in hormone levels affecting taste and smell,

avoidance will not lead to nutritional problems. How—

mood and emotional responses to foods, and inad—

ever, this assertion is based on a standard, Western

vertent control of pregnancy symptoms and con—

diet; for some vegan women, nuts may make a signif—

cerns for the growing fetus – are more likely to be

icant contribution to their energy and protein intake

the cause. Specific food-based advice may best be

and a useful contribution to their iron intake. Women

Section 3: Specialized requirements with a family history of allergies can be advised that Soy

alternative sources of protein include soy products,

Many meat and dairy substitutes (such as tofu, tex—

tempeh, seeds, beans, and pulses. The U.K. Commit—

tured vegetable protein, soy milk, and tempeh) are

tee on Toxicity has highlighted that although peanut

made from (or contain) soy beans. Soy naturally con—

allergic individuals may also clinically react to tree nut tains phytoestrogens, which can (weakly) mimic or

allergens, they generally do not react to other legumes, block the action of the human hormone, estrogen. It

such as green peas, soy beans, kidney beans, and lentils has been hypothesized that pregnant women who eat

[42].

soy might affect the future fertility of their babies.

Although nut avoidance may be prudent for some

However, the U.K. Food Standards Agency highlights

women, those without a family history of allergies

that this theory is based on animal studies, and there should be reassured that avoidance is not necessary for have not been any reports of problems in countries

them.

such as Japan where the traditional diet includes soy

[43] and average consumption is around 65 g per per-Impact of food safety advice son per day (mainly from tofu and miso) [44]. There has also been a single study that found an associa-Given that cheese and eggs may be important "station between maternal vegetarian diet and hypospa—

ples" in their everyday diet, LOVs may be concerned

dias [45]. The Food Standards Agency states that there about how standard food safety advice on the conis no need for pregnant women to avoid soy products sumption of these foods during pregnancy might affect

if they are eaten as part of a healthy balanced diet.

their dietary choices. Most developed countries rec—

Women hoping to obtain omega-3 from soy prod—

ommend that to avoid the risk of listeria (which is

ucts are likely to be disappointed. Although 7% to 8%

more common in pregnancy and can lead to prema—

of the fat contained in soy beans is ␣-linolenic acid

ture delivery, miscarriage, stillbirth, or serious health (ALA; omega-3), soya products, which mostly con—

problems for the newborn), pregnant women should

tain the isolated protein or protein concentrates and

avoid soft mold-ripened cheeses, such as camembert

are nearly fat free (such as defatted soya milks, flours, and brie, blue-veined cheeses (whether pasteurized or

and textured vegetable protein (TVP), are not good

unpasteurized), and any unpasteurized dairy products.

sources of these fatty acids. Furthermore partial hydro-Because cooking kills listeria, cooked dishes (served genation of soya oils reduces ␣-linolenic acid by 50%

piping hot) that contain these cheeses do not need

to 80% [44].

to be avoided. Vegetable paté should also be avoided.

Women can be assured that hard cheeses (such as

cheddar), feta, ricotta, mascarpone, cream cheese, cot-Supplements tage cheese, processed cheese, and cheese spread can

Vegetarian and vegan women may be more likely than

be eaten safely during pregnancy, as can live or bio

their peers to take dietary supplements [46]. In this yogurt, probiotic drinks, fromage frais, crème fraiche, light, key advice should ensure that any supplements

and sour cream.

they are taking contain folic acid and vitamin D and do Other pertinent advice for vegetarian women is

not contain vitamin A – in line with standard dietary

the importance of thoroughly washing any fruits, veg—

advice for pregnant women. As discussed earlier, a

etables, and pre-prepared salad leaves to reduce the

supplemental vitamin B12 may be advisable for vegan

risk of toxoplasmosis. Owing to the risk of salmonella, women, especially if they do not consume fortified

women are advised to avoid raw and partially cooked

products.

eggs and products that may contain them. In prac—

Some vegetarian and vegan women may seek

tice, this is likely to mean being cautious about

advice on the importance of consuming fish or tak—

home-or restaurant-cooked foods such as home—

ing fish oil supplements during pregnancy because of

made mayonnaise, salad dressing, or some desserts;

the proposed association between maternal omega—

products purchased from grocers will generally have

3 fatty acid consumption and cognitive function in

been made with pasteurized egg. Although there is

childhood [47]. Long-chain omega-3 fatty acids found advice not to give children aged under 1 year honey, in fish oils, particularly docosahexaenoic acid (DHA), there is no need for pregnant or lactating women to

are required for the normal development of the retina

avoid it.

and central nervous system [48], and it has been **Chapter 13: Vegetarians and vegans during pregnancy and lactation** suggested that pregnant and lactating women should for vegetarians, are also now available. Initial trials aim to achieve a daily intake of 200 mg of DHA [47].

show dose-dependent increases in plasma phospho—

However, the evidence for such an association is lim—

lipid and erythrocyte DHA levels [51], suggesting that ited. In addition, many fish oil supplements contain they may be a better option for vegetarians wishing

high amounts of vitamin A (although this is not

to supplement their diets with omega-3 fatty acids.

necessarily stated on the label), which can cause birth Although fish is obviously

not a normal part of vege—

defects.

tarian diets some women describing themselves as veg—

Plant foods generally contain no naturally

etarians may include it in their diets either occasion-occurring long-chain polyunsaturated fatty acids.

ally or regularly. Women who have no objection to fish Long-chain omega-3s can be synthesized from the

should be given the general advice to consume oily fish shorter-chain omega-3 ␣-linolenic acid found in

(e.g. salmon, sardine, mackerel) once or twice a week.

certain seeds, including flaxseed (linseed), walnut,

rapeseed (canola), and soy-bean oils, but only to a

Conclusions

limited extent. Levels of cord plasma and cord artery

Vegetarian diets can vary enormously in quality, and

phospholipid DHA, and also breast milk DHA, have

it cannot be assumed that a woman describing her—

been found to be lower among Hindu vegetarians

self as vegetarian has a diet that is any better or worse than nonvegetarians [11]. The long-term health than average. The degree of risk largely depends on implications for the infant of these differences in fatty how restrictive an individual’s diet is. Although the evi-acid intake and status are unclear. Several brands of dence base is limited, there are specific issues health omega-3 and -6 supplements, suitable for vegetarians,

professionals should consider when advising vegetar—

are available. These generally contain a combination

ian women during pregnancy or lactation. Because

of plant oils including flaxseed oil and oil of evening there are no specific evidence-based or clinical guide-primrose and advertise benefits to brain and general lines for vegetarian and vegan women, the best starting fetal and infant development. However, there is a lack point is to adapt existing guidance for all women.

of evidence to support such claims. A study in the

Because health professionals' and women's key

Netherlands found that supplementation with ALA

concerns may not tally, it is important to discuss with during pregnancy failed to improve neonatal DHA

a woman her individual concerns. Most LOV women

status [49]. Another study, in the United States, found can be reassured that, with some careful planning, that 20 g supplements of flax seeds during pregnancy

their diets should be adequate. For those who are fol—

did not increase the DHA content of breast milk

lowing more restrictive diets (such as those who do

[50].

not consume dairy products daily or eggs on a regu—

Part of the problem is that vegetarians tend to

lar basis), more effort will be required to ensure their have higher intakes of omega-6 fatty acids, including

nutrient requirements are met. For such women, con—

arachidonic acid, which reduces the synthesis of DHA

sumption of fortified foods and/or supplements is rec—

from ALA by competing for the desaturase enzymes.

ommended to ensure adequate intakes of iron, cal—

Reducing the ratio of LA to ALA is therefore advis—

cium, iodine, and vitamins B

able [48] and can be achieved by consuming less corn 12 and D.

and sunflower oils. High intakes of trans fats also

appear to interfere with the conversion of AA to DHA

This work represents the views of the authors only and may [48] and should be avoided. Supplements containing not reflect the views of the National Institute for Health and preformed DHA, derived from algal oils and suitable

Clinical Excellence.

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Chapter

14**Hyperemesisinpregnancy**

James D. Paauw and Alan T. Davis

Introduction

Hypersalivation, or ptyalism, is typical [19]. Elevated Nausea and vomiting during pregnancy are extremely serum concentrations of hepatic enzymes and sali—

common, presenting in 50% to 90% of all gravidas

vary amylase are not uncommon findings in HG, and

[1]. The most common presentation of this complex is abnormalities in thyroid function are seen in approxi-between the fourth and seventh weeks of pregnancy, mately 60% of patients [20–23].

when 70% of those affected develop symptoms [2].

A number of maternal complications have been

Vomiting abates in 90% of cases by the 16th week

associated with HG, including those related to the

of pregnancy [2]. A more severe variant associated physiology of vomiting, such as Mallory-Weiss syn-with greater morbidity, hyperemesis gravidarum (per-drome, esophageal rupture, retinal hemorrhage, pneu—

nicious vomiting of pregnancy), affects between 0.3%

mothorax, aspiration pneumonia, and splenic avulsion

and 2% of pregnancies [3–5]. Definitions of hypereme-

[24–26]. Possibly the most dangerous nutritional consis gravidarum (HG) vary considerably, but HG is best sequence related to HG is Wernicke's encephalopa—

described as vomiting in pregnancy that is sufficiently thy, which is a rare but potentially devastating com—

severe to produce weight loss, dehydration, starva—

plication caused by a deficiency of thiamine, an

tion ketoacidosis, alkalosis from loss of hydrochloric essential cofactor in carbohydrate metabolism. In the

acid in vomitus, and hypokalemia [6]. A transient rise presence of HG, thiamine deficiency is typically pre-in liver enzymes is seen in 15% to 25% of women cipitated by provision of glucose without concur—

who are hospitalized with HG [7]. Although the etiol-rent thiamine supplementation. In a recent review ogy of HG has not been identified, a number of fac—

of the 49 reported cases of HG-related Wernicke's

tors have been suggested as contributory, including

encephalopathy, 46.9% manifested all three of the clas-high or rapidly rising serum concentrations of serum sic triad of confusion (63.3%), ocular signs (95.9%)

chorionic gonadotropin or estrogens [8], seropositiv-and symptoms (57.1%), and ataxia (81.6%) [27]. The ity to Helicobacter pylori [9, 10], thyrotoxicosis [11,

mean gestational age at the presentation of these signs 12], upper gastrointestinal dysmotility [13], and psy-and symptoms was 14.3 weeks, after a mean dura-chological factors [14, 15]. Eating disorders have also tion of 7.7 weeks of nausea and vomiting. Diagno-been associated with HG [16, 17]. Goodwin has postu-sis is made clinically but can be rapidly confirmed lated that nausea and vomiting during pregnancy is not by magnetic resonance imaging. Complete remis—

a single condition but a syndrome with multiple poten—

sion occurred in only 28.6% of patients, with symp—

tial etiologies, such as vestibular mechanism, "back—

tom resolution requiring months. Permanent impair—

ground” gastrointestinal motility dysfunction, or hor—
ments were common. The overall pregnancy loss
monal sensitivity, among others, each of which may
rate (spontaneous and planned abortions) in HG
respond to a different targeted therapy [18].
patients with Wernicke’s encephalopathy was 47.9%.
The diagnosis of HG is made clinically after exclu—
The authors recommended provision of supplemental
sion of other causes. Onset of HG usually occurs
thiamine in prolonged vomiting of pregnancy, espe—
between the 4th and 10th weeks of gestation, with
cially before initiation of intravenous hydration or
associated progressive weight loss (≥ 5% of pre—
parenteral nutrition, and prompt thiamine replace—
pregnant body weight), ketosis, and dehydration in
ment if neurologic symptoms develop in patients with
association with abnormal serum electrolytes, includ—
HG. Other nutrition-related complications associated

ing hyponatremia, hypochloremia, and hypokalemia.
with HG, although uncommon, include coagulopathy

Chapter 14: Hyperemesis in pregnancy

as a result of vitamin K deficiency and peripheral neu-and vomiting were assessed for subjective response ropathy caused by deficiency of either vitamin B6 or

and number of emesis episodes after being ran—

B12 [28, 29].

domized to a 3-day trial with one of three treat—

The existence of economic consequences to HG has

ments: pyridoxine-metoclopramide, promethazine, or

also been established, with some authors attempting

prochlorperazine. Despite an initial lack of differ—

to quantify these effects. In patients with HG, 12%

ence in pretreatment symptoms, the women taking

discontinued employment altogether in one Swedish

pyridoxine-metoclopramide reported improved sub—

study, and one third (of 363 subjects) lost an average of jective response and fewer emesis episodes than those

62 hours of work between gestational Days 39 through

subjects receiving either of the two monotherapy

84 in a prospective investigation [30, 31].

treatments [36]. Continuous subcutaneous metoclopramide resulted in complete symptom resolution in 64% of subjects in a large retrospective study of HG

Treatment of hyperemesis gravidarum patients from a national database. Most of the side

Appropriate fluid, electrolyte, and vitamin resusci—

effects that were reported by approximately 30% of

tation is the initial treatment for HG. This regi—

the subjects were considered to be mild, and the

men includes generous supplementation of thiamine,

therapy had the added benefit of allowing for out—

as well as vitamin B6 (pyridoxine), which, although

patient treatment in most cases [37]. Odansetron is usually given in conjunction with antihistamines, also frequently used in refractory HG, although it is

has been found to ameliorate nausea and vomiting

not thought to be more effective than promethazine

of pregnancy by itself [32]. Adjunct pharmaceutical [38].

therapy to relieve nausea and vomiting commonly

Several newer antiemetics have been tried in the

includes promethazine, prochlorperazine, chlorpro—

treatment of resistant HG with some success, although

mazine, meclizine, droperidol-diphenhydramine, and

so far only in a few small studies. In a case series of metoclopramide. Extensive data show lack of ter—

six women treated for resistant HG with levomepro—

atogenic effects with histamine H1 receptor blockers

mazine, good symptomatic control was achieved in

(promethazine and cyclizine), phenothiazines (chlor—

each case [35]. Five of the pregnancies progressed to promazine and prochlorperazine), and dopamine the birth of live-born infants with no evidence of con-antagonists (metoclopramide and domperidone) [33,

genital anomaly, and the sixth pregnancy culminated

34]. Although evidence exists for a better pregnancy in an intrauterine death with no external or ultra-outcome from the use of antihistamines in HG, there sound evidence of congenital anomaly. Another case

is a consensus that withholding the use of these agents series reported the use of mirtazapine within the intra-until after the first 10 weeks of pregnancy is best. The venous fluid support for approximately 1 week in three literature contains a number of stepwise drug regi—

patients with severe HG who had previously failed

mens for the treatment of HG, all with some varia—

conventional treatment, including promethazine and

tion. A reasonable approach for the first line of ther-metoclopramide [39]. All responded to mirtazapine apy for HG consists of rehydration and maintenance within 24 hours, with resumption of diet within a

of fluid status, as necessary, with intravenous flu—

few days of initiation of this treatment. Each was

ids, thiamine supplementation, and choice of pyri—

reported to have no relapse of symptoms through—

doxine or promethazine as the antiemetic agent, with

out the pregnancy and delivered healthy newborns.

prochlorperazine serving as a second-line antiemetic

Such early results are promising in the development of therapy [35]. Patients with HG who fail these ther-these newer antiemetic agents as second-line drugs for apies are determined to have resistant HG, and a

the treatment of resistant HG. Large-scale prospective number of pharmaceuticals and modalities are being

randomized trials need to be undertaken to validate

studied in the further treatment of this group. Meto—

the efficacy of these therapies.

clopramide has become a common alternative to

Considerable discussion has centered on the use

conventional antiemetics, either alone or in com—

of corticosteroids for the treatment of the symptoms

bination with other agents, with promising enough

of HG. The genesis of this approach lies in the suc—

results to consider it as a second-line antiemetic. In cessful use of this modality for the treatment of nau—

one prospective trial, 174 women with first trimester

sea and vomiting due to cancer chemotherapy-induced

singleton pregnancies associated with severe nausea

emesis. Although some success has been reported, the

Section 3: Specialized requirements literature is variable with regard to the type, dose,

where from before conception to up to 7 weeks ges—

schedule, and route of corticosteroids to be employed

tation and were found to be significantly less symp—

in the treatment of HG, as well as outcome measures.

tomatic than a control group [46]. The authors con-Most studies to date seem to validate some usefulness cluded that preemptive therapy appears to be effective of corticosteroids in symptomatic relief of nausea and in preventing HG in subsequent pregnancies.

vomiting in HG. One week of daily 40 mg oral pred—

Several alternative therapies have been promoted

nisolone, or its intravenous equivalent as hydrocorti—

for use in patients with HG. There have been a num—

sone for those intolerant of the oral medication, led to ber of preliminary studies looking at the efficacy of

an improved sense of well-being, appetite, and weight

ginger in reducing the nausea and vomiting of preg—

gain compared with placebo controls and a trend

nancy. Although data are insufficient to recommend

toward improved nausea and vomiting [40]. A short ginger universally and there are concerns about prod-course of oral methylprednisolone with a 2-week taper uct quality due to the limited regulation of dietary

has been found to be more effective than promethazine

supplements, several literature reviews have suggested in effecting resolution of symptoms and resumption

that ginger appears to be a fairly low-risk and effec—

of eating, with the advantage of completing treatment

tive treatment for nausea and vomiting associated with in an outpatient setting [41]. Pulsed high-dose intra-pregnancy in patients not responding to traditional venous hydrocortisone was found to be significantly

first-line therapies [47, 48]. Although these authors more effective than regularly scheduled intravenous recommend further study of ginger, there has been vig—

metoclopramide in reducing vomiting episodes and

orous dissent for this suggestion on the grounds that

in preventing readmission in women with intractable

dietary supplements cannot be assumed to be safe for

hyperemesis [42]. Conversely, intravenous methyl-the embryo or fetus and that ginger, although possi-prednisolone followed by a prednisone taper did not bly effective, offers no advantage compared with med—

reduce the need for later rehospitalization compared

ications for which safety for the fetus has received

with placebo controls in women with HG who had

more extensive evaluation [49]. Despite this objection, failed outpatient therapy when both groups were also the American College of Obstetrics and Gynecology

receiving promethazine and metoclopramide [43].

guidelines currently recommend ginger as worth try—

When promethazine was compared with low-dose

ing for nausea and vomiting of pregnancy. In a study of prednisolone over 10 days, despite an early (48-hour)

the related issue of Internet advice offered by “medical advantage with promethazine, after completion of

herbalists” on the use of ginger, raspberry, and juniper treatment, the group receiving prednisolone experi—

in the nausea and vomiting of pregnancy, the authors

enced less nausea and fewer episodes of vomiting than

concluded that “the advice offered is misleading at best the promethazine group [44]. Both low-dose and high-and dangerous at worst,” with frequent omission of dose corticosteroids appear to bestow some treatment

any mention of potential side effects [50]. Two stud-advantage over other single entities in reducing symp-ies have found that multivitamins given at conception toms, as well as possibly limiting rehospitalization.

help reduce the severity of nausea and vomiting of

However, the differences seem to dissipate when cor—

pregnancy [51, 52]. These data offer a potential treat-ticosteroids are used concurrently with other agents.

ment option for planned pregnancies in women with

One caveat is that the presence of weight loss may

a past history of HG. Finally, in an intriguing study

be a determining factor in predicting success of cor—

of acupuncture plus acupressure in women with HG,

ticosteroids in prompting resolution of symptoms in

twice weekly sessions for 2 weeks was equally as effec-severe HG. Women who

have lost more than 5% of tive as metoclopramide with vitamin B12 in reducing

pre-pregnant weight uniformly manifest a successful

nausea intensity and vomiting, as well as improving the response to corticosteroids [45].

rate of food intake [53]. Although it bears noting that Because there is a high recurrence in subsequent metoclopramide also was given only twice weekly for 2

pregnancies in women who have previously experi—

weeks, acupuncture was found to be significantly more

enced HG, some clinicians advocate the use of preemp—

effective than drugs in improving ability to function in tive treatment in pregnant women with a past history

routine daily activities.

of HG. Women with previous HG who were identified

A representative summary of current treatment

before a subsequent planned pregnancy were prospec—

options is shown in Table 14.1, with the general order **140**

tively assigned to preemptive therapy beginning any—

of choice of treatment listed from top to bottom and

Chapter 14: Hyperemesis in pregnancy

Table 14.1 Current treatment options for hyperemesis

ber of authors have found no relationship [3, 56–58],

gravidarum

whereas other researchers describe evidence of a nega-

First-line therapy

tive effect of HG on infant birth weight [4, 59, 60]. Sev-Intravenous fluids, electrolytes, thiamine eral studies have shown that when confounding vari—

Pyridoxine

ables can be included in a multivariate analysis of the data, an initial apparent relationship of HG to reduced Promethazine

birth weight can be excluded [61, 62]. However, infants **Second-line therapy** born to hyperemetic mothers have a significantly lower Prochlorperazine

gestational age as well as a significantly longer length Metoclopramide, intravenous or subcutaneous

of hospital stay than infants born to control mothers

With or without pyridoxine

[61]. These outcomes support the need for aggressive **Pharmacotherapy in refractory hyperemesis gravidarum** treatment of HG during pregnancy, including nutrition support, where indicated.

Odansetron

In situations in which the symptomatology and

Corticosteroids

associated malnutrition of HG become severe, nutri—

2-week oral prednisolone/methylprednisolone (if initially tion intervention beyond manipulation of oral intake

tolerant)

is necessitated. The American Society of Parenteral and Intravenous hydrocortisone with oral taper (if initially intolerant) Enteral Nutrition (ASPEN) clinical guidelines strongly Levomepromazine

encourage the use of nutrition support in pregnant

Mirtazapine

women who are at increased risk of the complica-

Alternative therapy in refractory hyperemesis tions of malnutrition and to improve outcome for both

gravidarum

mother and infant [63]. Reports of enteral nutrition as Ginger a therapeutic modality for HG appeared contemporary

Acupuncture/acupressure

to the first reports, in the early 1980s, of the use of parenteral nutrition in the treatment of HG, but it appears to have fallen out of comparative favor, mainly because the most commonly accepted therapies listed higher in

of concerns of poor tolerance and promotion of recur—

each category.

rent symptoms [64, 65]. The use of enteral nutrition in the treatment of HG underwent a resurgence in the 1990s, not only as a source of nutrition but as a modal-Hyperemesis gravidarum and nutrition ity to alleviate the nausea and vomiting of HG [66–68].

It has been understood for some time that women

The nasogastric route seems to be the most effective

suffering from HG are at high risk for malnutrition,

route of enteral nutrition in reducing the nausea and

whether monitored by percentage of body loss or by

vomiting of HG in patients in whom these symptoms

serum markers of nutriture [54, 55]. The risks of mater-are associated with the consumption of food [66]. It is nal malnutrition in pregnancy and associated com-thought that smell and tactile sensations promote the plications, both maternal and fetal, are well known,

symptoms of nausea and vomiting in these patients,

and the literature is replete with these. The controversy such that bypassing the oral cavity with a nasogastric regarding malnutrition in HG relates not to its exis —

tube minimizes these gustatory and olfactory cues. In

tence but to its effect on the outcome of pregnancy.

a detailed report of seven women with meal-related

There has been an ongoing debate over whether HG

nausea and vomiting of HG, nasogastric feeds suc—

has any effect on pregnancy outcome and, if so, the

cessfully alleviated these symptoms within 24 hours in magnitude of that effect. Inherent in this debate is

each subject [68]. Oral liquids were tolerated within 2

whether the nature and extent of therapy and, in parto 5 days of feeding tube placement, and all patients

ticular, nutrition intervention, ameliorates an effect of were discharged within 8 days of initiation of enteral HG on pregnancy outcome. It is clear that maternal

nutrition (mean = 4.6 days), six on outpatient enteral weight loss should be minimized in HG, because it is

nutrition. All patients were eventually able to dis—

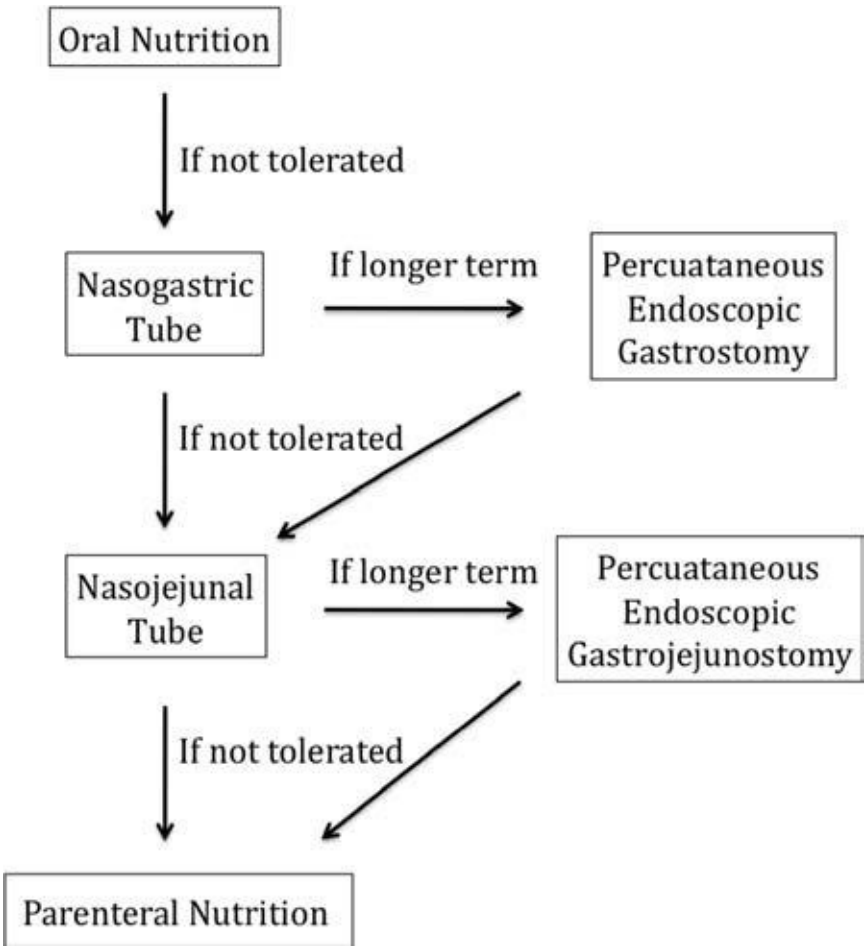
an independent predictor of poor fetal outcome [55].

continue enteral nutrition prior to delivery (mean =

Conflicting data exist in the literature with regard to 43 days). The authors stress that the key to success-

an association between HG and birth weight. A num—

ful enteral nutrition in HG is patient stabilization with



Section 3: Specialized requirements appropriate hydration and electrolyte balance first. In follow-up to this report, van de Ven noted that an

iso-osmotic solution is recommended in this situation, with periodic aspiration of the stomach to prevent gastric retention and pulmonary aspiration [69].

Because the presence of a long-term nasogastric

tube may be somewhat onerous to a patient, a gastrostomy tube can be placed instead. The first two reported cases of percutaneous endoscopic gastrostomy (PEG)

in conscious pregnant women supported the safety of

this modality as well as favorable maternal and fetal

outcomes [70].

Jejunal feeding may be necessary in HG patients

who are intolerant of gastric feeding. Nasojejunal tubes can be placed either endoscopically or fluoroscopically with appropriate shielding [71, 72]. Patients with HG

refractory to standard treatment with intravenous fluids and antiemetics undergoing nasojejunal feeding

had relatively rapid improvement in nausea and vomiting and were able to have their feeding tubes removed

when they were well enough to take more than 1000

Figure 14.1 Algorithm for preference of route of nutrition support calories orally (4–21 days) [71]. Several case reports of in hyperemesis gravidarum.

the use of PEG with a jejunal port (PEGJ) have demonstrated that this technique is a safe, effective, and relatively cost-effective intervention for severe refractory sis, pneumothorax, intrahepatic cholestasis, placental HG [73, 74].

fatty infiltration, and catheter dislodgement [80, 81].

There has been some debate over which technique

At least one maternal-fetal death has been reported

(nasogastric tube, PEG, or PEGJ) is the preferred route as a complication of parenteral nutrition in pregnancy of enteral nutrition in patients with severe refractory [82]. The complication rate of parenteral nutrition in nausea and vomiting of HG [75, 76]. Inherent with pregnancy can be reduced by the use of peripherally enteral nutrition by PEGJ is the necessity of giving

inserted central catheters (PICC), but the incidence

feedings in a continuous or cyclic fashion to avoid

of line-related sepsis alone, which is generally inde—

the usual jejunal intolerance of bolus feeding. In the pendent of type of venous

catheter used, is approxi—

current absence of prospective, randomized controlled

mately 25% [80, 83]. In addition, the HG patient is trials, it makes empiric sense to first give a trial of at high risk for central catheter-related thromboem—

nasogastric enteral nutrition in patients with refrac—

bolism through a combination of the elevated coagu—

tory HG. If symptoms improve but prolonged enteral

lopathy factors associated with pregnancy and dehy—

nutrition becomes necessary, a PEG should be con—

dration contributing to venous stasis. In nonpregnant

sidered for longer-term support. However, if there is

adult patients, the incidence of Doppler ultrasound–

intolerance for nasogastric feedings, a trial of nasoje-detected PICC-related upper extremity venous throm—

junal feedings would be prudent before placing a PEGJ.

bosis was found to be 62% in patients not prophy—

In the face of the complete failure of enteral nutrition, laxed with anticoagulants and remained 23% in those

initiation of parenteral nutrition would become neces—

who were prophylaxed with some type of anticoag—

sary.

ulation [84]. These are not insignificant values given The use of parenteral nutrition in pregnancy, in that pregnant patients are almost certainly at a higher

general, and in HG, specifically, has been reported for risk of venous thromboembolic disease than the gen—

more than 25 years, with successful outcomes [77–80].

eral population. Given the risk of complications related However, it is clear that the use of parenteral nutrition to use of parenteral nutrition in pregnancy, as well as in pregnancy is associated with a variety of maternal

the previously noted significant cost differential rela-142

complications, including infection, venous thrombo—

tive to enteral nutrition, parenteral nutrition should

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be used only under established, documented criteria

should have failed all earlier steps in the decision—

in patients with HG. These criteria include weight loss making tree shown earlier. Parenteral nutrition in

over a time period of at least 4 weeks, failed conser—

HG should be considered a “therapy of exclusion,”

vative therapy (including intravenous hydration and a

that is, resorted to only after all other options have variety of antiemetic medications), and persistent lab-been exhausted. Figure 14.1 summarizes the prefer-oratory findings, such as serum electrolyte abnormali-ences for the route of nutrition support in a treatment ties and hypoalbuminemia [83]. In addition, patients algorithm.

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Chapter

15**Multiplepregnancy**

Barbara Luke

In 2004, there were 139,494 infants born from multi—

Multiple pregnancy represents a state of magnified

ple pregnancies in the United States, the highest num—

nutritional requirements, resulting in a greater nutriber ever recorded [1]. Since 1980, there has been a 93%

ent drain on maternal resources and an accelerated

increase in the incidence of twins and a 544% increase depletion of nutritional reserves. The accelerated star-in triplet and higher-order multiples (quadruplets and vation that occurs in pregnancy is exaggerated with

quintuplets). The primary factors contributing to this a multiple gestation,

particularly during the second

change have been the widespread use and availabil—

half of pregnancy, with more rapid depletion of glyco—

ity of infertility treatments, in combination with the gen stores and resultant metabolism of fat between

trend of childbearing at older ages. Although infants of meals and during an overnight fast. A reduced glu—

multiple births account for only approximately 3% of

cose stream from mother to fetus results in slower

all live births, they are disproportionately represented fetal growth and smaller birth size, as well as a higher among the preterm (Ↄ 37 weeks, 16%), very preterm

risk of preterm labor and preterm birth. For this rea-

(Ↄ 32 weeks, 22%), low birth weight (Ↄ 2500 g, 32%),

son, diet therapy with a diabetic regimen of 20% of

and very low birth weight (Ↄ 1500 g, 27%) infant pop—

calories from protein, 40% of calories from carbohy—

ulations. The average birth weight and gestational age drate, and 40% of calories from fat may be partic—

is 3316 g at 38.7 weeks for singletons, compared with

ularly useful. Iron-deficiency anemia has also been

2333 g at 35.2 weeks for twins, 1700 g at 32.1 weeks for linked to preterm delivery and other adverse preg—

triplets, 1276 g at 29.7 weeks for quadruplets, and 1103

nancy outcomes. Maternal iron status, in addition to

g at 28.4 weeks for quintuplets [1]. An estimated 19%

the amount and pattern of gestational weight gain,

of all neonatal intensive care unit days are associated is an important factor associated with fetal growth

with multiple pregnancies [2].

and length of gestation in twin pregnancies. Supple—

The population of women pregnant with multiple

mentation with calcium, magnesium, and zinc, as well

gestations is distinctly different from the average pregas multivitamins and essential fatty acids, may also nant woman in the United States (Table 15.1). Over reduce pregnancy complications and improve post-the past 20 years, there has been a growing trend in natal health for infants born from a multiple gesta—

delaying pregnancy; this pattern is magnified among

tion. Diet therapy for women pregnant with multi—

women pregnant with multiples. Although the per—

ples is an important component of effective prenatal

cent of women aged 35 and older having a singleton

care. The majority of studies to date have evaluated

baby has increased threefold since 1980, the percent

the effects of nutritional factors on the course and out-having twins has increased nearly fourfold, and those come of singleton pregnancies; the body of literature

having triplets or higher-order births nearly sixfold

on multiple gestations is growing, but there are still [1]. Although older maternal age may be associated many gaps in our knowledge of normal and abnormal with better financial and social resources, from a phys-physiological changes and effective interventions. The iological perspective, the special nutritional demands following chapter summarizes current research on

of a multiple pregnancy have important implications

maternal pregravid weight, gestational weight gain,

for the mother’s future health. For example, when a

carbohydrate metabolism, iron status, and vitamin and

woman has a multiple pregnancy in her 40s or 50s,

mineral intake on fetal growth and length of gestation she may be within only a few years of menopause, and

in singletons and, when known, in twin and triplet ges-the substantial calcium drain may increase her risk for tations.

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osteoporosis [3].

Section 3: Specialized requirements Table 15.1 Live births by maternal age, birth order, and plurality, United States, 1980, 1990, and 2004

Birth

Percent of

order

births maternal

and year

Number of births by maternal age (years) age (year)

All Ages

Ↄ20

20–24

25–29

30–34

35–39

≥40

≥30

≥35

≥40

First births

1980

1 545 604

435 333

605 183

371 859

112 964

18 241

2 024

8.6

1.3

0.1

1990

1 689 118

401 900

515 455

465 458

230 612

66 541

9152

18.1

4.5

0.5

2004

1 630 921

336 783

483 752

395 784

279 884

110 418

24 300

25.4

8.3

1.5

All births

1980

3 612 258

562 330

1 226 200

1 108 291

550 354

140 793

24 290

19.8

4.6

0.7

1990

4 158 212

533 483

1 093 730

1 277 108

886 063

317 583

50 245

30.2

8.8

1.2

2004

4 112 052

422 043

1 034 454

1 104 485

965 663

475 606

109 801

37.8

14.2

2.6

Plurality and year singletons

1980

3 478 715

545 958

1 184 408

1 064 764

526 049

134 294

23 242

19.7

4.5

0.7

1990

4 061 319

525 793

1 072 431

1 246 144

860 478

307 498

48 975

30.0

8.8

1.2

2004

3 972 558

415 327

1 010 421

1 069 417

924 160

450 733

102 500

37.2

13.9

2.6

Twins

1980

68 339

7 212

21 374

22 712

12 944

3559

538

24.9

6.0

0.8

1990

93 865

7 605

20 945

30 020

24 466

9587

1242

37.6

11.5

1.3

2004

132 219

6 629

23 602

33 315

38 751

23 088

6834

51.9

22.6

5.2

Triplets and more

1980

1337

83

385

474

321

67

7

29.5

5.5

0.5

1990

3028

85

354

944

1119

498

28

54.3

17.4

0.9

2004

7275

87

431

1753

2752

1785

467

68.8

31.0

6.4

All multiples

1980

69 676

7295

21 759

23 186

13 265

3626

545

25.0

6.0

0.8

1990

96 893

7690

21 299

30 964

25 585

10 085

1270

38.1

11.7

1.3

2004

139 494

6716

24 033

35 068

41 503

24 873

7301

52.8

23.1

5.2

Carbohydrate metabolism

been linked to an increase in preterm labor and

Pregnancy is a state of accelerated starvation, result-preterm delivery, a phenomenon termed the “Yom ing in lower fasting glucose levels and an exag—

Kippur effect” [5]. A reduced glucose stream from geration of the insulin response to eating. In twin mother to fetus results in slower fetal growth, smaller pregnancies, these changes are magnified, particu—

birth size, and an increased risk of fetal growth restric-larly during the second half of pregnancy, with sig—

tion [6]. The diet therapy we have used successfully nificantly lower maternal serum glucose and insulin in both twin and triplet pregnancies is based on the

concentrations and higher plasma concentrations of

diabetic regimen of three meals and three snacks per

-hydroxybutyrate compared with maternal concen—

day (Table 15.2). We have found in studies with both trations in singleton pregnancies, indicating more twins and triplets [7, 8] that diet therapy with 20%

rapid depletion of glycogen stores and resultant

of calories from protein, but a lower percentage of

metabolism of fat between meals and during an

calories from carbohydrate (40%) for better glycemic

overnight fast [4]. Both fasting and ketonuria have control, and a higher percentage of calories from fat **148**

Chapter 15: Multiple pregnancy

Table 15.2 Body mass index (BMI)-specific dietary recommendations for twin gestations **Under Normal**

Over

BMI Group

weight

weight

weight

Obese

BMI range

Ↄ19.8

19.8–26.0

26.1–29.0

Ↄ29.0

Calories

4000

3500

3250

3000

Protein (20% of calories)

200 g

175 g

163 g

150 g

Carbohydrate (40% of calories)

400 g

350 g

325 g

300 g

Fat (40% of calories)

178 g

156 g

144 g

133 g

Exchanges (servings) per day

Dairy

10

8

8

8

Grains

12

10

8

8

Meat and meat equivalents

10

10

8

6

Eggs

2

2

2

2

Vegetables

5

4

4

4

Fruits

8

7

6

6

Fats and oils

7

6

5

5

Adapted from Luke B, Brown MB, Misiunas R, Anderson E, Nugent C, van de Ven C, Burpee B, Gogliotti S. Specialized prenatal care and maternal and infant outcomes in twin pregnancy.

Am J Obstet Gynecol (2003), 189:934–8.

(40%), to provide additional calories with less bulk, are encouraged as well, such as iron-fortified breads and

most effective. The emphasis is also on the use of low grains, vegetables, and nuts.

glycemic index carbohydrates to prevent wide fluctua—

The few studies that have evaluated iron status in

tions in blood glucose concentrations.

multiple pregnancies have reported lower hemoglobin

levels in the first and second trimesters, higher rates of iron-deficiency anemia, and even residual iron-

Iron status

deficiency anemia in the infants, up to 6 months of age Iron-deficiency anemia is also significantly associated [14–16]. Hediger and Luke [17] reported that by the with preterm delivery [9–11]. Serum ferritin levels, third trimester, lower levels of serum ferritin (indicat-which are lowered with iron deficiency and elevated ing better volume expansion) were significantly asso—

in the presence of infection, have also been linked

ciated with pregravid body mass index (BMI) and rate

to prematurity. Extremes of maternal serum ferritin

of weight gain to 20 weeks. Serial measures of iron sta-levels measured early in the second trimester (15–17

tus (hemoglobin [Hgb], hematocrit [Hct]) and mea—

weeks), as well as elevated levels at 24, 26, or 28 weeks, sures of maternal nutritional status, including weight have been associated with preterm birth [12, 13]. Ele-gain, were collected for 293 twin pregnancies. As in vated third trimester serum ferritin levels are signifi-singleton pregnancies, levels of Hgb and Hct declined cantly associated with preterm and very preterm birth, through the first trimester to a nadir at 20 to 24

with iron-deficiency anemia and poor maternal nutri—

weeks. Consistent with greater volume expansion in

tional status underlying the relationship [13]. Dietary twin pregnancies, the levels were even lower in the sec-sources of iron are preferable, particularly hem-iron-ond trimester than for singleton pregnancies. By the rich sources such as red meat, pork, poultry, fish, and third trimester, lower levels of serum ferritin (indicat-eggs, because of better absorption and utilization, their ing better volume expansion) were associated with pre—

positive effect on non-hem-iron bioavailability, and

gravid BMI (−0.50 ± 0.21 g/l per kg, p = 0.02) and

their high quality and quantity of protein and other

rate of weight gain to 20 weeks (−11.6 ± 5.0 g/l per kg nutrients. The inclusion of non-hem-iron sources is

weight gain, p = 0.02). As shown in prior studies, both **149**

Section 3: Specialized requirements maternal pregravid BMI and rate of weight gain before

ommended Dietary Allowance [RDA] for pregnancy)

20 weeks are consistently strong predictors of twin

was associated with an increased incidence of iron—

birth weight outcomes. Mean levels by trimester were

deficiency anemia at entry to care, a lower use of prena-as follows: tal supplements during pregnancy, and a higher inci—

First

Second

Third

dence of inadequate weight gain during pregnancy, as

Trimester

Trimester

Trimester

well as an increased risk of low birth weight, preterm Hemoglobin

12.8 g/dL

11.3 g/dL

11.0 g/dL

delivery, and early preterm delivery. The joint effect Hematocrit

37.3%

32.8%

32.0%

of iron-deficiency anemia at entry to care and a low

Ferritin

56.6 g/L

34.3 g/L

12.2 g/L

dietary zinc intake during pregnancy increased the risk of preterm delivery fivefold.

Iron status during pregnancy has also been linked to

fetal programming and the development of chronic

Multivitamin and multimineral

disease. Low maternal hemoglobin is strongly related

to the development of a large placenta and high pla-

supplementation

cental:birth weight ratio, which is seen as predictive of Ideally, pregnant women should get the level and range long-term programming of hypertension and cardio—

of required nutrients through a balanced diet. National vascular disease. Because the iron demands of preg—

dietary surveys indicate, however, that adult women

nancy may exceed 1 g, with nearly half this amount

fail to meet the RDAs for five nutrients: calcium, mag-in the red cell mass increase in blood volume, the nesium, zinc, and vitamins E and B6 [27]. In addition, maternal preconceptional and early pregnancy iron prenatal use of vitamin-mineral supplements among

status are extremely important. Severe maternal iron—

low-income women has been shown to reduce the

deficiency anemia leads to placental adaptive hyper—

risks of preterm delivery and low birth weight, partic-trophy, a fall in the cortisol metabolizing system, ularly if initiated during the first trimester [28]. Sup-and increased susceptibility to hypertension in later plementation in excess of twice the RDA should be

life.

avoided because of the potential for birth defects. The fat-soluble vitamins, particularly vitamins A and D,

Calcium, magnesium, and zinc

are the most potentially toxic during pregnancy. The

supplementation

pediatric and obstetric literature includes case reports of kidney malformations in children whose mothers

Calcium, magnesium, and zinc have been identified

took between 40 000 and 50 000 IU of vitamin A dur—

by the World Health Organization as having the

ing pregnancy. Even at lower doses, excessive amounts

most potential for reducing pregnancy complications

of vitamin A may cause subtle damage to the devel—

and improving outcomes [18, 19]. Results of calcium oping nervous system, resulting in serious behavioral supplementation trials among high-risk women have

and learning disabilities in later life. The margin of been promising, with significant reductions in preterm safety for vitamin D is smaller for this vitamin than for deliveries among teenagers and women with low—

any other. Birth defects of the heart, particularly aor-calcium diets [20, 21]. Magnesium may have a neuro-tic stenosis, have been reported in both humans and protective role, particularly for the premature infant.

experimental animals with doses as low as 4000 IU,

Although maternal zinc nutriture has been signifi—

which is 10 times the RDA during pregnancy. These

cantly related to length of gestation, infection, and

recommendations are for singleton pregnancies but

risk of premature rupture of membranes [22, 23],

are applicable to multiple pregnancies as well.

clinical trials of zinc supplementation have yielded

equivocal results [24]. A trial that randomly supplemented only women with plasma zinc levels below **Essential fatty acid requirements**

the median reported an increase in length of gesta—

There is an established maternal drain of the essen—

tion of approximately 0.5 week and an increase in birth tial fatty acids during pregnancy, particularly during weight (approximately half of which was explained by

multiple gestation [29, 30]. Additional supplementa-the longer duration of gestation) [25]. Scholl *et al.* [26]

tion with omega-3 fatty acids, which are vital for neu-reported that a low dietary zinc intake during single—

rological and retinal development, may be particularly **150**

ton pregnancy (≤ 6 mg/day or Ↄ 40% of the Rec—

beneficial during pregnancy for both the mother and

Chapter 15: Multiple pregnancy

Table 15.3 Optimal rates of maternal weight gain and cumulative gain by pregravid body mass index (BMI) status **Rates of weight gain (kg/week)** **Cumulative weight gain (kg)**

Pregravid BMI

0–20 weeks

20–28 weeks

29 weeks–delivery

To 20 weeks

To 28 weeks

To 36–38 weeks

Underweight

0.57–0.79

0.68–0.79

0.57

11.3–15.9

16.8–22.2

22.7–28.1

(BMI < 19.8)

Normal weight

0.45–0.68

0.57–0.79

0.45

9.1–13.6

13.6–20.0

18.1–24.5

(BMI 19.8–26.0)

Overweight

0.45–0.57

0.45–0.68

0.45

9.1–11.3

12.7–16.8

17.2–21.3

(BMI 26.1–29.0)

Obese

0.34–0.45

0.34–0.57

0.34

6.8–9.1

9.5–13.6

13.2–17.2

(BMI Ċ29.0)

Results are from models controlling for diabetes and gestational diabetes, preeclampsia, smoking during pregnancy, parity, placental membranes, and fetal growth before 20 weeks.

Adapted from Luke B, Hediger ML, Nugent C, Newman RB, Mauldin JG, Witter FR, O'Sullivan MJ. Body mass index specific – weight gains associated with optimal birthweights in twin pregnancies. J Reprod Med (2003), 48:217–24.

her developing baby. Populations with a higher intake

even greater effect on twin birth weight, with gains to of omega-3 fatty acids have significantly lower rates

20 weeks, between 20 and 28 weeks, and from 28 weeks

of preterm delivery and low birth weight [31]. Infants to birth increasing birth weights by 65 g, 37 g, and 16 g, whose mothers had higher omega-3 fatty acid levels at

respectively, per kilogram per week of maternal weight birth demonstrated better cognitive development [32].

gain [35–37].

One of the newest prenatal supplements incorporates

BMI-specific weight gain guidelines are associated

omega-3 fatty acids in its formulation (Duet DHA by

with the best intrauterine growth and subsequent birth StuartNatal).

weights, and longer length of gestation [38, 39], but studies among women pregnant with singletons [40,

41] and twins [42] have reported that more than one **Maternal weight gain** fourth of women receive no advice regarding weight

The pattern of maternal weight gain has been shown

gain. Among women who do receive guidance, for

to be as important as total weight gain in its effect

more than one third of women, the advice they receive

on birth weight in both singleton and twin pregnan—

is inappropriate [40]. We have developed BMI-specific cies. Although the increase in fetal weight is great-guidelines for twins based on optimal rates of fetal est during the third trimester (after 28 weeks), gains growth and birth weights between the singleton 50th

during mid-gestation (either second trimester or 20–

percentile and twin 90th percentile at 36 to 38 weeks

28 weeks) have the strongest association with birth

(2700–2800 g)[43] (Table 15.3).

weight. In singletons, Abrams and Selvin [33] demon-The effect of higher weight gain before 20 or 24

strated that birth weight increased in each trimester by weeks on twin and triplet birth weight is most pro—

18 g, 33 g, and 17 g, respectively, per kilogram per week nounced among infants of underweight gravidas [35,

of maternal weight gain. Scholl *et al.* [34] reported that 44]. This early weight gain may reflect the acquisition weight gains to 20 weeks and to 28 weeks were most of maternal nutrient stores, particularly the deposition strongly related to birth weight, contributing 22 to 24

of body fat [45]. In addition, levels of fat-mobilizing g to birth weight per kilogram per week of maternal hormones, such as follicle-stimulating hormone (FSH)

weight gain. In addition, a low rate of weight gain or and human placental lactogen (hPL), may be higher in

a poor pattern of weight gain is associated with an

normal-weight and overweight women, as well as in

increased risk of preterm birth. Studies in twins by

women with dizygotic twin pregnancies [46]. There-our research team have shown similar results, with low fore, underweight women with low early weight gain

weight gains consistently associated with reduced birth may be lacking appropriate nutrient reserves (includ-

weights. Early and mid-gestation weight gains exert an ing maternal stored fat) as well as adequate levels

 of hormones to mobilize those nutrient stores that

periods of maternal weight gain for average triplet

are available, resulting in a high incidence of fetal

birth weight were from conception to 20 weeks and

growth restriction. Higher early gains may be partic—

between 20 and 28 weeks (351 g/kg/week, p = 0.001,

ularly important in multiple pregnancies for two dis—

and 247 g/kg/week, p = 0.001, respectively); for aver—

tinct reasons. First, pregnancy is usually much shorter age triplet birth weight, z scores were between 20 and for multiple gestations, by as much as 4 to 12 weeks,

28 weeks (1.17 SD units/kg/week, p Ↄ 0.0001); and

thereby shortening the period for intrauterine growth.

for length of gestation from 28 weeks to delivery (10.1

As shown by Williams *et al.* [47], the peak rate of days/kg/week, p Ↄ 0.0001).

growth in weight for multiples occurs at about 31

weeks compared with 33 weeks for singletons. Sec-

Key clinical points

ond, higher gains during early gestation may influence r

the structural and functional development of the pla—

The primary factor contributing to the rise in

centa [48]. In multiple pregnancies, the placenta ages multiple births has been the widespread use and more quickly, shortening the gestational period during availability of infertility treatments, in

which it can most effectively transfer nutrients to the combination with the trend of childbearing at

developing fetuses. Higher gains during early gesta—

older ages.

tion may therefore initially benefit placental structure r The average birth weight at gestational age is 3316

and function, and subsequently augment fetal growth

g at 38.7 weeks for singletons, compared with 2333

through more effective placental function as well as the g at 35.2 weeks for twins, 1700 g at 32.1 weeks for

transfer of a higher level of nutrients.

triplets, 1276 g at 29.7 weeks for quadruplets, and

In their analysis of 1138 triplet pregnancies, Elster

1103 g at 28.4 weeks for quintuplets.

et al. [49] reported several factors to be predictive r The accelerated starvation is exaggerated with a of higher average fetal weight for a given gestational multiple gestation, and therefore diet therapy with

age, including male sex, older maternal age, mater-a diabetic regimen of 20% of calories from

nal height, pregravid weight and weight gain, and

protein, 40% of calories from carbohydrate,

parity. These investigators also reported that length

and 40% of calories from fat is particularly

of gestation correlated with maternal age, parity, and effective.

weight gain. Maternal weight gain was even more

r The pattern of maternal weight gain has been

strongly associated with outcomes in triplets than

shown to be as important as total weight gain in

in twins, and gains in different periods of gestation

its effect on birth weight in both singleton and

affected birth weight, birthweight-for-gestation (birth twin pregnancies. BMI-specific weight gain

weight z score), and length of gestation as demon—

guidelines are associated with the best

strated in a study of 144 triplets by Luke *et al.* [7].

intrauterine growth and subsequent birth weights,

Regression analyses indicated that the most significant as well as longer length of gestation.

Chapter 15: Multiple pregnancy

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Chapter

16 Mineral and vitamin supplementation before, during, and after conception

Y. Ingrid Goh

Adequate quantities of vitamins and minerals are

acid, or no supplementation. Supplementation com—

essential for the development of the embryo, fetus,

menced 1 month before conception and continued

and neonate. These substances are involved in cell

through the first 12 weeks of pregnancy. Supplemen—

growth and differentiation and are central compo—

tation with multivitamin containing folic acid resulted nents of cell structure, cell signaling, protein transla-in 3 of 256 (1.17%) children with NTD, whereas no

tion, enzymes, catalytic enzyme sites, and enzymatic

supplementation resulted in 11 of 260 (4.23%) chil—

reactions. Together, these processes are critical for

dren born with NTD [7]. A 72% protective effect organ development in the fetus. The critical period of was associated with folic acid supplementation (rel—

organogenesis occurs at 20 to 60 days gestation [1, 2].

ative risk [RR] = 0.28, 95% confidence interval [CI]

The brain, however, is especially vulnerable to nutri—

0.12–0.71) [7]. A meta-analysis of the available litera-tional insults because it develops through the entire ture observed that folic acid–containing multivitamins course of pregnancy and after birth. Deficiencies in

resulted in an odds ratio (OR) = 0.67, 95% CI 0.58–

vitamins and minerals may result in a disruption of

0.77 in case-control studies and an OR = 0.52, 95% CI

normal development, leading to undesirable outcomes

0.39–0.69 in cohort and randomized controlled studies

such as increased rates of spontaneous abortion, con-

(Table 16.1) [8].

genital malformation, or fetal death. This chapter high-Multivitamin supplementation has also been asso—

lights the importance of vitamin and mineral supple—

ciated with decreased risk for other congenital mal—

mentation before, during, and after conception. It is

formations including oral clefts and congenital heart

important to note that although the following studies

defects (CHDs) [6, 9–11]. A retrospective study of discuss the use of multivitamins, multivitamins vary in women who delivered a child with oral cleft observed

composition from study to study, which may have an

a 3.1% incidence in the multivitamin-supplemented

overall influence on the effects.

mothers, whereas a 4.8% incidence was observed in

The importance of multivitamin supplementation

unsupplemented mothers [9]. Another case-control during pregnancy dates back to the 1960s, when a study observed a 50% decrease in cleft palate with cleft case-control study by Smithells demonstrated that pre—

lip (OR = 0.5, 95% CI 0.36–0.68) and a 27% decrease

natal multivitamin supplementation was protective

in cleft palate without cleft lip (OR = 0.73, 95% CI

against neural tube defects (NTDs) [3]. A large cohort 0.46–1.2) with multivitamin supplementation [12]. A study by Milunsky *et al.* also observed a decreased meta-analysis of the available literature observed that incidence of NTDs (1.1/1 000 multivitamin supple—

supplementation with prenatal multivitamins resulted

mented vs. 3.5/1 000 unsupplemented) [4]. Several in an OR = 0.76, 95% CI 0.62–0.93 of cleft palate studies published by Czeizel *et al.* indicate that folic in case-control studies and an OR = 0.42, 95% CI

acid–containing multivitamins are associated with a

0.06–2.84 in cohort and randomized controlled stud—

decreased risk of NTDs [5, 6]. However, the most sig-ies (Table 16.1) [8]. This was similar for oral cleft with nificant trial demonstrating this relationship was a or without cleft palate: OR = 0.63, 95% CI 0.54–0.73

multicenter randomized double-blinded trial headed

in case-control studies and OR = 0.58, 95% CI 0.28–

by the United Kingdom Medical Research Council

1.19 for cohort and randomized controlled studies

[7]. In this study 1817 women who had previously (Table 16.1) [8]. These protective effects were con-delivered a child with an NTD were randomized to firmed by a meta-analysis in which vitamin sup—

one of four treatments: folic acid (4 mg), folic acid

plementation was associated with reduction in the

(4 mg) and a multivitamin, multivitamin without folic

incidence of cleft lip and palate (RR = 0.51, 95%

Section 3: Specialized requirements Table 16.1 Dietary reference intakes recommended for pregnant individuals **Case-control Cohort and randomized control trial** Neural tube defect

OR = 0.67, 95% CI 0.58–0.77

OR = 0.52, 95% CI 0.39–0.69

Cleft palate

OR = 0.76, 95% CI 0.62–0.93

OR = 0.42, 95% CI 0.06–2.84

Cleft lip without palate

OR = 0.63, 95% CI 0.54–0.73

OR = 0.58, 95% CI 0.28–1.19

Urinary tract anomalies

OR = 0.48, 95% CI 0.30–0.76

OR = 0.68, 95% CI 0.35–1.31

Cardiovascular defects

OR = 0.78, 95% CI 0.67–0.92

OR = 0.61, 95% CI 0.40–0.92

Limb defects

OR = 0.57, 95% CI 0.38–0.85

OR = 0.25, 95% CI 0.05–1.15

Congenital hydrocephalus

OR = 0.37, 95% CI 0.24–0.56

OR = 1.54, 95% CI 0.53–4.50

From Goh YI, Bollano E, Einarson TR, Koren G, Prenatal multivitamin supplementation and rates of congenital anomalies: a meta-analysis. J Obstet Gynaecol Can (2006), 28:680–9.

CI 0.32–0.95), cleft palate (RR = 1.19, 95% CI 0.43–

of the pelvic-ureteric junction was observed in chil—

3.28), and all clefts (RR = 0.55, 95% CI 0.32–0.95) in dren born to women who took prenatal multivitamins

prospective studies; cleft lip and palate (RR = 0.77,

(OR = 0.19, 95% CI 0.04–0.86) [6]. A meta-analysis 95% CI 0.65–0.90), cleft palate (RR = 0.80, 95% CI 0.6– of the available literature observed that supplementa—

0.93), and all clefts (RR = 0.78, 95% CI 0.71–0.85) in tion with prenatal multivitamins resulted in an OR =

case-control studies [13].

0.48, 95% CI 0.30–0.76 in case-control studies, and OR

Several studies by Czeizel *et al.* observed that folic = 0.68, 95% CI 0.35–1.31 in cohort and randomized

acid–containing multivitamins decreased the occur—

controlled studies [8].

rence of CHDs (RR = 0.48, 95% CI 0.23–1.03) in

Czeizel *et al.* observed that the incidence of

one study and (OR = 0.60, 95% CI 0.38–0.96) in

limbs defects was lower in women who supplemented

another [6, 14]. Botto *et al.* observed decreased rates with multivitamins compared with unsupplemented as well (RR = 0.48, 95% CI 0.20–0.89) [15]. Prenatal women [5]. Shaw *et al.* also observed that supplemen-multivitamin supplementation was specifically asso-tation with multivitamins was associated with a 35%

ciated with a decreased occurrence of heart defect

decrease in limb defects (OR = 0.65, 95% CI 0.43–

(OR = 1.8, 95% CI 1.4–2.4), tricuspid atresia (OR =

0.99) [11]. A meta-analysis of the available literature 5.2), obstructive defects

(OR = 2.7), transposition of observed that supplementation with prenatal multivi—

great arteries (OR = 1.9), and ventral septal defect

tamins resulted in an OR = 0.48, 95% CI 0.30–0.76 in

(OR = 1.8) compared with unsupplemented moth—

case control studies, and OR = 0.57, 95% CI 0.38–0.85

ers [16]. A meta-analysis of the available literature in cohort and randomized controlled studies [8].

observed that supplementation with prenatal multivi—

The literature regarding the relationship of prena—

tamins resulted in a decreased association of cardio—

tal multivitamin supplementation and omphalocele,

vascular defects in both case-control studies (OR =

pyloric stenosis, and imperforate anus is limited. One 0.78, 95% CI 0.67–0.92) and cohort and randomized

case-control study observed that multivitamin sup—

controlled studies (OR = 0.61, 95% CI 0.40–0.92) [8].

plementation was associated with a 60% reduction in

Studies investigating the effects of prenatal mul—

nonsyndromic omphalocele (OR = 0.4, 95% CI 0.2–

tivitamin supplementation on urinary tract develop—

1.0) [19]. A study by Czeizel *et al.* observed a lower ment observed a 78% reduced risk for urinary tract incidence of hyperpyloric stenosis in women with

pre—

anomalies compared with the unsupplemented group

natal multivitamin supplementation compared with

(RR = 0.22, 95% CI 0.05–0.99) [17]. A retrospective women without supplementation [5]. This protec-case-control study observed that supplementation in tive effect, however, was not observed by Correa—

the first trimester was associated with an 85% reduc—

Villase˜nor *et al.* [20]. One study observed that prena-tion in risk of having a child with urinary tract anoma-tal multivitamin supplementation was associated with lies (OR = 0.15, 95% CI 0.05–0.43); the most notice—

a 50% decrease in imperforate anus [21].

able decrease was that of hydronephrosis (OR

= 0.12,

Prenatal

multivitamin

supplementation

has

95% CI 0.04–0.38) [18]. A reduction in stenosis/atresia also been associated with decreasing the risk for **Chapter 16: Mineral and vitamin supplementation before, during, and after conception** pediatric cancers [22–24]. Several studies have been resulted in an OR = 0.53, 95% CI 0.42–0.68 for neu-published associating prenatal multivitamin supple-roblastoma [28].

mentation with the decrease of pediatric brain tumors.

Prenatal multivitamin has been shown to have ben—

Preston-Martin *et al.* were the first to observe this efits for both human immunodeficiency virus (HIV)-

relationship (OR = 0.6, p = 0.12) [22]. These results infected women and their babies. A double-blinded were supported by findings by Bunin *et al.* (OR = 0.56, trial demonstrated that HIV-1-infected women receiv—

p = 0.02) [25]. Primitive neuroectodermal tumors ing multivitamins had a higher hemoglobin concen-

(PNET), specifically, were noted to decrease with

tration than women who did not receive multivitamins

prenatal multivitamin supplementation (OR = 0.38,

(p = 0.07) [33]. In addition, they had a 63% lower p = 0.005) [25]. An additional study by this group risk of macrocytic anemia (RR = 0.37, 95% CI 0.18– further noted that supplementation was associated

0.79, p = 0.01), and children also had reduced risk

with a decreased risk of astrocytoma [26]. Further of anemia [33]. Supplementation was also associated confirmation of these findings of decreased PNET and with a decreased incidence of low birth weight (RR

astrocytoma was observed in the studies by Preston-

= 0.82; 95% CI 0.70–0.95; p = 0.01), lower rates of

Martin *et al.* [23] An international study of more than fetal death (RR = 0.87; 95% CI 0.72–1.05; p = 0.15), 1 000 women observed that prenatal multivitamin

reduction in the risk of a birth size that was small for supplementation in the first two trimesters of preg—

gestational age (RR = 0.77; 95% CI 0.68–0.87; p Ↄ

nancy was associated with a decreased risk for brain

0.001), increase in Psychomotor Development Index

tumors in children aged under 5 years (OR = 0.7,

score of 2.6 in children aged 6 to 18 months (95% confi-95% CI 0.5–0.9) [24]. Moreover, a greater reduction dence interval 0.1–5.1), reduction in the development was observed when supplementation occurred over

of hypertension during pregnancy (RR = 0.62, 95% CI

all three trimesters of pregnancy (OR = 0.5, 95% CI

0.40–0.94, p = 0.03), reduction in maternal mortality, 0.3–0.8) [24]. A retrospective population-based study reduction in risk of progression of HIV to Stage IV

observed that prenatal multivitamin supplementation

disease, and reduction in early-child mortality among

was associated with a decreased risk of medulloblas—

immunologically and nutritionally comprised women

tomas [27]. A meta-analysis of the available literature [34–37].

observed that folic acid containing multivitamins

There are different risk groups for vitamin defi—

resulted in an OR = 0.73, 95% CI 0.60–0.88 for

ciency in pregnancy, including genetic factors and con-pediatric brain tumors [28].

comitant medications. Genetic factors that may result

Some studies have also suggested that prenatal

in malabsorption of vitamins and minerals include

multivitamins decrease the risk for acute lymphoblas—

genetic mutations; maternal disease including liver,

tic leukemia (ALL) [29, 30]. A case-control study by renal, cancer, gastrointestinal, diabetes, and cancer; Sarasua and Savitz observed that prenatal multivita—

concomitant medications; and interactions with other

min supplementation was associated with a decreased

vitamins and minerals. Drugs that may alter mater—

risk for ALL [29]. A decrease in ALL was also observed nal levels of multivitamins include methotrexate and in a case-control study by Wen *et al.* (OR = 0.7, 99%

valproic acid.

CI 0.5–1.0) [30]. Ross *et al.* also noted that multivita-Women actively planning pregnancy should sup-min supplementation was associated with a decreased plement with a prenatal multivitamin. Supplementa—

risk for ALL (OR = 0.51, 95% CI 0.30–0.89). A meta—

tion to prevent birth defects has been shown to be cost-analysis of the available literature observed that folic effective [38–41]. Supplementation should commence acid–containing multivitamins resulted in an OR =

approximately 3 to 4 months before the planned preg—

0.61, 95% CI 0.50–0.74 for ALL [28].

nancy to permit the body to achieve protective lev—

Prenatal multivitamin supplementation has also

els of vitamins and minerals such as folate. This, how-been associated with a decreased risk for neurob—

ever, may be difficult because 50% of pregnancies are

lastoma [31, 32]. A case-control study by Michalek unplanned [42]. A possible solution to this dilemma *et al.* reported a decreased risk for neuroblastoma is to encourage women of childbearing potential to

(OR = 0.28, 95% CI 0.03–0.69) [31], as did a case-incorporate multivitamin supplementation into their control study by Olshan *et al.* (OR = 0.6, 95% CI daily routine.

0.4–0.9) [32]. A meta-analysis of the available litera-Some women believe that multivitamin supple-157

ture observed that folic acid–containing multivitamins mentation is required only in the first trimester of

Section 3: Specialized requirements Table 16.2 Dietary reference intakes recommended for

vitamin B2 (riboflavin), vitamin B3 (niacin), vitamin

pregnant individuals

B5 (pantothenic acid), vitamin B6 (pyridoxine), vita-

Micronutrient

Dietary reference intakes

min B9 (folic acid), vitamin B12 (cyanocobalamin),

vitamin C (ascorbic acid), vitamin D, vitamin E, cal—

Vitamin A (retinol)

770 g/day

cium, chromium, copper, iodine, iron, magnesium,

Vitamin B1 (thiamine)

1.4 mg/day

manganese, molybdenum, selenium, and zinc (Table

Vitamin B2 (riboflavin)

1.4 mg/day

16.2). The following sections review their importance

Vitamin B3 (niacin)

18 mg/day

during pregnancy.

Vitamin B5 (pantothenic acid) 6 mg/day

Vitamin B

Vitamin A

6 (pyridoxine)

1.9 mg/day

Vitamin B9 (folate)

600 g/day

Vitamin A is a fat-soluble, antioxidant vitamin that

Vitamin B

is important in growth, epithelial tissue proliferation, 12 (cobalamin)

2.6 mg/day

and vision. Vitamin A is an important component of

Vitamin C (ascorbic acid)

85 mg/day

photoreceptor cells, and as such it is important for

Vitamin D

5 g/day

the development of the eyes. Vitamin A deficiency

Vitamin E (tocopherol)

15 mg/day

results in irreversible impairment or loss of vision

Source: Dietary Reference Intakes: Recommended Intakes for in 250 000 to 500 000 preschool-aged children in the

Individuals (PDF 87 KB) (Washington, DC: Food and Nutri-Third World annually [43, 44]. Vitamin A and its syn-tion Board, Institute of Medicine, National Academy of Sciences, 2004). Available at: http://www.iom.edu/Object.File/

thetic congeners, the retinoids, have been proven to

Master/21/372/0.pdf.

be active human teratogens. The minimum teratogenic

dose during pregnancy has not been established, and

thus doses exceeding the recommended daily amount

pregnancy. This is untrue. Supplementation should,

(RDA) should be avoided. Vitamin A is transported

as previously mentioned, commence before pregnancy

and stored in a nontoxic protein-bound form. Con—

and continue through the entire pregnancy and dur—

genital malformations are seen only when the storage

ing lactation. It is true that the first trimester is a capacity of 25 000 to 50 000 IU is exceeded. High expo-critical time for structural formation of the fetus.

sure of vitamin A in utero can result in retinoid syn—

However, during the second and third trimesters, the

drome. This is characterized by central nervous sys—

brain of the fetus is continually forming, and the

tem malformation, cardiovascular malformations, and

fetus itself is growing at a rapid pace. As such, ade—

musculoskeletal abnormalities [45]. A study compar-quate macronutrient supply during the entire preg-ing women consuming 8 000 to 25 000 IU with those nancy is necessary. Moreover, supplementation should

who had less than 5 000 IU vitamin A daily observed

continue after pregnancy into the period of lactation.

no increased risk for malformations (OR = 0.73, 95%

In cases in which the mother is unable to attain a

CI 0.27–1.96) or cranial neural crest defects (OR =

well-balanced diet (e.g. for medical, socioeconomic,

1.09, 95% CI 0.24–4.98) compared with the control

physical, or emotional reasons), multivitamin supple—

group [46]. Conversely, a study by Rothman *et al.*

mentation will assist her in achieving a balance of vita-reported that women who ingested more than 10 000

mins and minerals regardless of her dietary habits. For IU per day of vitamin A supplements had an increased

instance, calcium and vitamin D will assist in the main-risk for delivering a child with a congenital malformatenance of bone mineral density. Supplementing with tion [47]. Dietary sources of vitamin A include animal-multivitamins will also help replenish nutrients neces-derived products such as eggs, liver, meat, and fruits sary for the production of blood to replenish blood that and vegetables containing beta-carotene.

is lost during delivery. Moreover, multivitamin supplementation during lactation will ensure that the baby is being breast-fed milk containing sufficient nutrients **Vitamin B1 (thiamine)**

(Table 16.2).

Vitamin B1 is a water-soluble vitamin essential for

The formulations of prenatal multivitamins usu—

metabolism of carbohydrates as well as for nerve

ally vary between manufacturers; however, they gen—

and heart function. Pregnant women have substan—

erally comprise a combination including vitamin A

tially greater than normal need for vitamin B

1 [48].

(beta-carotene and/or acetate), vitamin B1 (thiamine), Deficiency in this vitamin may arise from inadequate

 dietary intake, increased dietary requirements, hyper-ful in the management of nausea and vomiting dur-emesis gravidarum, and malabsorption

due to gas—

ing pregnancy [57]. Dietary sources of vitamin B6

trointestinal disorders, alcohol abuse, HIV, genetic

include bananas, carrots, nuts, fish, liver, and whole factors, or drugs [49]. Lower vitamin B1 content grains.

in blood cells has been observed in fetuses with

severe intrauterine growth retardation versus controls [50, 51]. Dietary sources of vitamin B

Vitamin B

1 include

9 (folic acid)

cereal products, brewer’s yeast, meat, poultry, and

Vitamin B9 is a water-soluble vitamin that is essen—

legumes.

tial in the formation of red blood cells and genetic

material. Folic acid is required for the synthesis of

Vitamin B

methionine from homocysteine [58]. Methionine is a **2 (riboflavin)** cofactor for many methylation reactions including the

Vitamin B2 is a water-soluble vitamin that is essential methylation of deoxyribonucleic acid (DNA), ribonu—

for the metabolism of carbohydrates and amino acids.

cleic acid (RNA), proteins, and neurotransmitters [59–

It also integral for tissue respiration and indirectly 62]. Therefore, all new-cell formation is dependent maintains erythrocyte integrity. Riboflavin has been on an adequate supply of folic acid. Folate deficiency positively correlated with fetal growth [52]. Dietary in rapidly dividing cells may lead to alterations in sources of riboflavin include liver, almonds, soy nuts, DNA synthesis and chromosomal aberrations, result—

shellfish, eggs, and dairy products.

ing in impaired cell formation and tissue growth; con—

sequently maternal folate requirements increase dur-

Vitamin B3 (niacin)

ing pregnancy [60, 63, 64].

Vitamin B3 is a water-soluble vitamin. It is metab—

Folic acid has long been known to decrease the

olized to niacinamide, an essential component of

risk of NTDs. One small double-blinded trial random—

nicotinamide adenine dinucleotide (NAD) and nico—

ized women who had previously delivered a child with

tinamide adenine dinucleotide phosphate (NADP)

NTD to receive 4 mg folic acid supplementation or

coenzymes for glycogenesis, tissue respiration, and

placebo [65]. In none of the 44 children were NTDs lipid metabolism. One study suggested that pericon-observed in the supplemented group, whereas 6 of 61

ceptional intake of vitamin B3 decreased the risk of

NTDs were observed in the unsupplemented group

orofacial clefts [53]. Dietary sources of vitamin B3

[65]. Similarly, an observational study reported a 0 in include meat, nuts, and cereals.

227 recurrence of NTDs in a folic acid–supplemented

group, whereas 2 in 213 NTDs were observed in the

Vitamin B

unsupplemented group [66]. A cohort study of women **5 (pantothenic acid)** supplementing with 5 mg of folic acid also observed no Pantothenic acid is a water-soluble vitamin that is

recurrence of NTDs in supplemented women, whereas

an important component of the coenzyme A in the

a 3% recurrence was observed in unsupplemented

transfer of acyl groups in the oxidation and synthe—

women [67]. Many other trials have examined the sis of fatty acids and in the metabolism of carbohy-effect of folic acid during pregnancy and have also drates, fats, and proteins [54]. Elevated circulating lev-observed a reduction in risk for NTDs [68, 69].

els of pantothenic acid are detected in the fetus [55].

To investigate whether the dosage of folic acid

Maternal pantothenic acid deficiency can result in ter-affects the rate of reduction of NTDs, the California atogenic effects [55]. Animal studies have also sug-Birth Defects Monitoring Program conducted a case-gested protection against NTDs [56]. Dietary sources control study comparing 538 children with NTDs and of pantothenic acid include liver, beef, and sunflower 540 controls [70]. Women who reported any use of seeds.

folic acid from 3 months before or 3 months after conception had an overall

lower risk of having a child

Vitamin B6 (pyridoxine)

with NTDs (OR = 0.60, 95% CI 0.46–0.79) [70].

Vitamin B6 is a water-soluble vitamin that is essen—

Women taking folic acid 0.4 to 0.9 mg had a fur—

tial for the metabolism of amino acids and fatty acids ther reduced risk. Women who supplemented with

for normal nerve function and formation of antibod—

less than 0.4 mg did not have important reductions

159

ies and red blood cells. Vitamin B6 has been help—

in risk (OR = 0.99) [70]. The only available study **Section 3: Specialized requirements** investigating serum folate concentrations found an

they are pregnant who have not begun supplement—

inverse relation between maternal cell folate and the

ing may benefit from supplementing with 5 mg of folic

risk of NTD [71]. Daly *et al.* showed in a case-control acid in their multivitamin to increase the available study that women receiving less than 150 g or more

folate in their bloodstream quickly. One manufacturer

than 400 g of folic acid had a 6.6 in 1 000 and 0.8 in has already begun manufacturing a prenatal multivita—

1 000 chance of delivering a child with NTD, respec—

min contain 5 mg folic acid, which can be purchased by tively [72].

Supplementation at different doses of 100

prescription. Dietary sources of folate include fortified g, 200 g, and 400 g resulted in a 22%, 41%, and

grains and green leafy vegetables.

47% decreased risk in NTD, respectively [72]. Another study investigating dosing variations of folic acid cor-roborated this result, noting that 100 g, 200 g, and **Vitamin B12 (cobalamin)**

400 g folic acid decreased NTD by 18%, 35%, and

Vitamin B12 is a water-soluble vitamin required

53%, respectively [73].

for growth, cell production, DNA synthesis, and

An interventional time series analysis observed a

erythropoiesis. Cobalamin is a cofactor in folate—

0.157 in 1 000 to 0.062 in 1 000 decrease in the inci-dependent homocysteine metabolism. It is involved dence of neuroblastoma after the introduction of folic in the methylation of homocysteine to form methio—

acid fortification of flour with an adjusted incidence nine and tetrahydrofolate as well as the conver-

(RR = 0.38, 95% CI 0.23–0.62) [74]. Not only is folic sion of methylmalonyl-coenzyme A to succinyl-acid beneficial in decreasing the risk for birth defects, coenzyme A [92]. Humans are unable to synthesize it can also treat anemia during pregnancy [75] and cobalamin [93]. Vitamin B12 deficiency can result in decrease the risk of premature births [76].

defective DNA synthesis, reduced rate of cell multipli-Folic acid is especially important for women cation, and metabolism disorders, which may lead to

who are using folate antagonists (e.g. valproic acid, a megaloblastic anemia or neurological abnormalities methotrexate) or have medical conditions (e.g. celiac [94, 95].

disease) in which folate is poorly absorbed. Women

Vitamin B12 deficiency is uncommon because

using folate antagonists are generally recommended

dietary requirements are usually met with the omniv—

to use 5 mg of folate. Some people have questioned

orous diet, and the vitamin is conserved efficiently by whether folic acid is associated with an increased rate enterohepatic circulation [96]. Cobalamin deficiency of cancers. Studies have suggested that it is protective may occur because of low dietary intake (strict veg—

against some cancers [77–85]. Because folic acid plays etarian diets) but also because of disturbance of the an important role in the cell cycle, theoretically, if all absorption, transport, or cellular uptake or genetic cells were healthy, then there would not be an issue. It is variations in transcobalamin II [97, 98]. Vitamin B12

only if there are cancerous cells that folate would assist deficiency has been associated with folate deficiency in their replication. However, the majority of existing (methyl-folate trap) [99–101].

literature supports a relationship of cancer protection.

A steady fall in serum cobalamin level has been

The minimum recommendation by health authori—

shown throughout pregnancy [102]. This fall is raties is 0.4 mg folic acid supplementation for pregnancy tionalized by increase plasma volume, changes in hor-

[86–88]. Studies of folic acid dosing have ranged up to monal status, and increased vitamin requirements 10 mg during pregnancy without any reported adverse

[103]. During pregnancy, blood homocysteine lev-events. Recently the U.S. Centers for Disease Control els decrease during the first and second trimesters

and Prevention and a Canadian study reported that

and slightly increase during the third trimester [104].

women of childbearing age did not have protective lev-Deficiency may result in hyperhomocysteinemia [92,

els of folate in their blood [89, 90]. Daly *et al.* showed 105].

that protective levels should be 900 nM folate [72]. In Hyperhomocysteinemia has been associated with light of this information, it has been suggested that the several pregnancy complications including repeated

current requirements of folic acid should be increased miscarriages [106, 107], preeclampsia [108, 109],

to 5 mg in prenatal multivitamins [91]. Previous stud-abruptio placentae [110, 111], NTDs [112–115],

ies of women receiving 5 mg of folic acid reported no intrauterine growth retardation [111, 116], and fetal adverse effects toward the fetus [67]. Because half of death [111]. It is also hypothesized that hyperhomo-160

pregnancies are unplanned, women discovering that

cysteinemia may increase the risk for megaloblastic

Chapter 16: Mineral and vitamin supplementation before, during, and after conception anemia and neuropsychiatric symptoms, which may ences [130]. Another study of mothers treated with occur even before the onset of megaloblastic anemia 0.25 to 3.25 g/day calcitriol (1,25(OH)2D3, a vita-

[117–120] and thrombosis in pregnancy and postpar-min D analogue) for hypoparathyroidism observed no tum [121, 122]. Dietary sources of vitamin B12 include adverse effects in the babies [131]. Daily vitamin D

liver, dairy products, and fortified cereals.

requirements can be met with adequate sun/ultraviolet light exposure.

Vitamin C (ascorbic acid)

Vitamin E (tocopherol)

Vitamin C is a water-soluble vitamin required for

Vitamin E is a fat-soluble vitamin that is important in collagen formation for bone and connective tissue

maintaining the integrity of the cell membrane, and

and various other metabolic processes, including the it protects cells against oxidative damage by free radi-conversion of folic acid to folinic acid and iron cals. Four double-blinded trials in women at high risk metabolism. In addition, this antioxidant maintains

of preeclampsia randomized participants to receive

the mechanical strength of amniotic membranes and

high doses of vitamin E (400–800 IU) in the second

assists in the absorption of iron.

and third trimesters of pregnancy [126, 132, 133]. No Pregnant women exposed to less than 2 000 mg difference was observed between supplemented and

vitamin C reported no adverse effects [123]. A meta-unsupplemented women for the risk of stillbirth, peri-analysis of vitamin C in pregnancy revealed simi—

natal death, preterm birth, intrauterine growth restric-lar results [124]. One study suggested an association, or mean birth weight [134]. One study reported tion between low maternal ascorbic acid levels and that concentrations of vitamin E were positively related increased frequency of premature rupture of amni—

to increased fetal growth [135].

otic membranes [125]. This prompted investigations Vitamin C and vitamin E have a synergistic effect of vitamin C in preventing preeclampsia. High doses

as antioxidants. High doses of vitamin C and vita—

of vitamin C and vitamin E in combination to treat

min E were used in combination to treat preeclampsia.

preeclampsia initially suggested a protective effect Recently it was shown that this combination may result [126]. However, this combination has recently been in low birth weight [128]. A cohort study of women associated with low birth

weight [127, 128]. One exposed to 400 to 1 200 IU of vitamin E during the study suggested that this effect may be due to vita—

first trimester of pregnancy observed no significant min E [129]. Further studies need to be undertaken to differences in rates of live births, preterm deliveries, determine the effects of vitamin C during pregnancy.

miscarriages, stillbirths, or malformations. There was, Dietary sources of vitamin C include oranges, fruits, however, an apparent decrease in mean birth weight

and vegetables.

in the supplemented group compared with controls

(p = 0.001) [129]. Dietary sources of vitamin E include **Vitamin D**

wheat germ oil, sunflower oil, green leafy vegetables, and peanuts.

Vitamin D is a fat-soluble vitamin required for the

absorption of calcium and phosphorus. A study of

15 mothers supplementing with vitamin D to treat

Conclusion

hypoparathyroidism observed that 107 000 IU daily

Prenatal multivitamin supplementation is beneficial to did not increase the risk for malformations, and

the development of the fetus, and therefore, women

follow-up at 16 years of age also observed no differactively planning pregnancy should supplement daily.

periconceptional supplementation

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Chapter

17**Determinantsofeggandembryoquality: long-term effects of maternal diet and assisted reproduction**

Kevin D. Sinclair and Wing Yee Kwong

Introduction

recognized that these early stages of development may be the most environmentally sensitive [11, 12].

Reproductive rate in humans is in decline, while the Consequently, set in the context of pregnancy

incidence of obesity and metabolic-related diseases

establishment and long-term developmental program—

are increasing. Recent World Bank statistics reveal

ming, this chapter provides a contemporary overview

that, although the pace of decline in reproductive

of the key developmental processes that take place

rate over the past 50 years differs between regions, during the earliest stages of mammalian development, this phenomenon is global, occurring in both devel—

highlighting their sensitivity to environmental influ-oped and developing countries. Statistics based on ences in a manner that can determine fertility, preg-the U.S. government's Centers for Disease Control nancy outcome, and offspring health.

and Prevention's National Center for Health Statistics, for the period 1960 to 2002, confirm these

trends in the United States [1]. Similarly, although **Ovarian folliculogenesis and oocyte** the proportion of clinically obese individuals is great-maturation est in developed countries, the problem of obesity

and obesity-related diseases is increasing most rapidly In sexually mature adults, the process of ovarian fol-in developing countries [2]. These trends in human liculogenesis, from when primordial follicles leave health can largely be attributed to changing lifestyles their resting state to when they reach the preovula—

but may also be due to environmental exposure to

tory stage, typically takes between 6 and 7 months,

endocrine-disrupting chemicals and, of particular rel-although the active period of growth is estimated to be evance to this chapter, diet at key stages during early around 12 weeks [14] and witnesses a 400-fold increase development [3–5].

in follicle volume [14] (Figure 17.1). Although the cor-At this juncture, the discussion could develop responding increase in oocyte volume (40-fold) may

in one of two ways. There is compelling evidence

appear more modest, it nevertheless represents a sig-that exposure in utero to environmentally prevalent nificant increase in mass and highlights the extent of endocrine-disrupting chemicals can lead to impaired

cellular biosynthesis that takes place in the germ cell reproductive development and the programming of

during this period of development. It further empha—

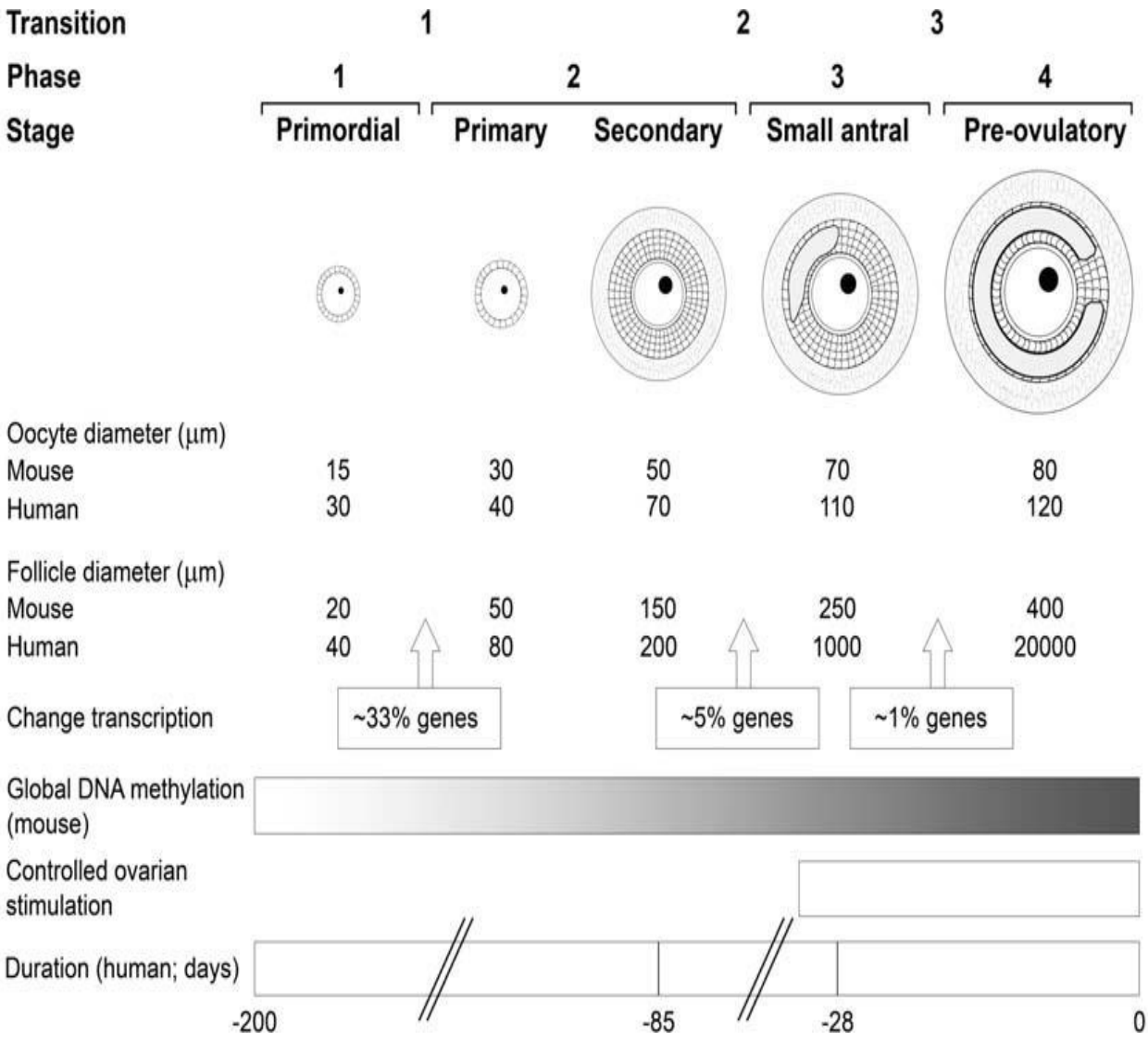
obesity and related metabolic disorders in animals and sizes the protracted period of time during which envi-humans. These topics have been extensively reviewed ronmental determinants of egg quality can exert their elsewhere [6–8]. Similarly, there is compelling evi-effects.

dence, from both epidemiological studies in humans

and direct interventionist studies with animals, that Transcriptional activity and DNA

many late-onset adult diseases arise as a consequence of malnutrition during in utero life [9], although direct methylation effects on fecundity are less clear [10]. Although most Transcript profiling during mouse oocyte develop-studies to date have investigated these effects during ment has revealed the primordial-to-primary follicle the greater part of pregnancy and infancy, much less transition to be a major transitional stage; changes attention has been directed toward understanding the in transcriptional activity, observed for approximately effects of environment and diet on the mammalian egg 33% oocyte genes, were greater at this than at any

and preimplantation embryo, although it is now widely other stage of folliculogenesis [15] (Figure 17.1).



Section 3: Specialized requirements Figure 17.1 Schematic representation of ovarian folliculogenesis and oocyte growth in the postnatal mouse and sexually mature human, highlighting molecular events that occur during each of three key transitionary periods.

A second major change in transcriptional activity

although at present these are poorly characterized in occurs between the secondary and tertiary (small

the germline [18]. The available evidence points to a antral) stages of follicular development. Here tran-genomewide loss of DNA methylation before meiotic scriptional activity is altered in fewer (∼5%) genes, arrest, although this is

thought to vary among single but many are associated with DNA synthesis and cell

copy genes and repetitive sequences. Remethylation

cycle regulation. Oocytes from preantral follicles are of the female germline occurs during oocyte growth

incapable of resuming meiosis, whereas oocytes from

(Figure 17.1), but much of our knowledge on the tim-small antral follicles have acquired this capacity [16].

ing of this process is limited to the remethylation

A third key transitional event occurs during antral fol-of a group of imprinted genes and repeat sequences licle development (coincident with follicular selection in the mouse [19]. Although the precise timing of and dominance in mono-ovular species). Although methylation acquisition varied between genes in that transcriptional activity was altered in only approxi-study, the most active period of DNA methylation was mately 1% of mouse genes [15], once again they were around 15 days post conception, coincident with the mostly genes involved in cell cycle progression and

formation of antral follicles. More recent studies in chromatin remodeling. The proportion of oocytes that the mouse and sheep, using an immunofluorescence

successfully reach metaphase II, and develop following staining approach to measure global DNA methyla—

fertilization, progressively increases with antral folli-tion, have since identified the most rapid phase of DNA cle size [17], indicating that significant “maturational”

methylation to occur in growing oocytes around the

events occur during the latter stages of antral follicle time of antrum formation in the follicle [20, 21].

development.

The temporal patterns of transcript expression

Ovarian stimulation and oocyte maturation

described here are integrally linked to ongoing epigeThe foregoing discussion highlights how key molec-

netic modifications to DNA and associated proteins,

ular events change in the days and weeks leading up

 to conception. Given that a typical in vitro

ally impaired and pregnancy rates following transfer fertilization (IVF) cycle, involving the use of

reduced [26]. However, it has seldom been possible to gonadotropin-releasing hormone (GnRH) agonists separate the effects of IVM from those of in vitro fer- and gonadotrophins, can last 3 to 4 weeks, it follows tilization or culture (discussed later).

that some of these molecular events may be disturbed in a manner that could jeopardize pregnancy outcome. A number of animal studies (albeit mostly with Maternal diet and egg quality

mice) support this premise. For example, using an

Because of the dramatic increase in obesity levels

immunostaining approach with an antibody against

referred to earlier, a considerable amount of research 5-methyl cytosine, Shi and Haaf [22] showed that the effort has been devoted to understanding the effects of DNA methylation pattern of two-cell mouse embryos

obesity on fertility. Overweight women are more likely differed between superovulated and nonstimulated

to encounter menstrual dysfunction and anovulation

females. Abnormal patterns of DNA methylation were

[27]. Furthermore, women with a body mass index associated with reduced preimplantation develop-25 kg/m−2 or greater have a lower chance of pregnancy ment in vitro. More recently, superovulation followed following IVF and have an increased miscarriage rate by in vivo development (i.e. embryo transfer to

[28]. A contributing factor in these cases is impaired pseudopregnant females) led to aberrant patterns of egg quality associated with insulin resistance. Much methylation and a loss of imprinting at specific loci in of the human data in this area is derived from patients midgestation mouse placenta [23]. There is an emerg-with PCOS [29]. We have shown that antral follicle ing consensus that trophectoderm-derived tissues development and egg quality are both impaired in

may be more susceptible to loss of imprinting than the clinically obese and hyperinsulinemic young female

embryo proper. Importantly, the results of that study cattle [30]. In that study, oocytes were retrieved from indicated that it is not the establishment of imprinting donors using ultrasound-guided follicular aspira—

that is affected but rather its maintenance. However, tion and matured, fertilized, and cultured in vitro.

this may merely reflect the timing of intervention. The Detailed analysis revealed that the negative relation-methylation status of several imprinted genes has also ship between insulin and egg quality (defined as the been reported in oocytes from stimulated and non—

proportion of inseminated oocytes that developed to

stimulated cycles in both the human and mouse [24].

the blastocyst stage) increased over time (Figure 17.2).

Modest gains in methylation at the H19 differentially This effect could be due to the duration of exposure of methylated region were observed in some oocytes

oocytes to elevated levels of insulin but also suggests from both species, although in the case of human

that oocytes exposed to high levels of insulin during oocytes, the effects of superovulation could not be

the preantral stages of follicular development may

distinguished from those of donor age and fertility.

be most sensitive. Recently, the ability of insulin—

The biological significance of these latter observations sensitizing agents 5-aminoimidazole 4-carboxamide—

is therefore uncertain, and there is generally a lack of riboside (AICAR), sodium salicylate, and rosiglita—

compelling evidence of a significant clinical problem zone to enhance the postfertilization developmental

in human pregnancies following ovarian stimulation

potential of oocytes was determined in obese C57BL/6

[25]. Poor perinatal outcomes in ovarian stimulated mice offered a high-fat diet [31]. Rosiglitazone, IVF cycles can often be explained by the confounding a potent agonist for the nuclear receptor peroxi—

factors of advanced maternal age and subfertility.

some proliferator-activated receptor gamma (PPAR

Similar reservations relate to statistics on preg—

gamma), was most effective in lowering blood insulin nancy and perinatal outcomes following in vitro mat—

and triglyceride concentrations and restoring postfer-uration (IVM). In many instances the retrieval of tilization development of in vivo–derived zygotes cul-germinal vesicle-stage oocytes for IVM is performed tured in vitro. Within the

mouse ovary, PPAR gamma

in women for whom polycystic ovarian syndrome

is most highly expressed in granulosa cells [32], where (PCOS) has been diagnosed, so that the effects of it can interact with target genes such as Cd36 and

IVM cannot be separated from the underlying causes

Scarb1 involved in lipid uptake and metabolism [31].

of subfertility [25]. Long-term developmental conse-PCOS is a heterogeneous syndrome affecting quences of IVM have been largely unexplored in ani—

5% to 10% of women of reproductive age and is

169

mal studies, but postfertilization development is usu-generally characterized by oligo-anovulation, clinical **Section 3: Specialized requirements** Oestrous cycle

Figure 17.2 Regression coefficients for

blastocysts of cleaved against plasma insulin

1

2

3

concentrations determined at each of two

0.1

oocyte recovery sessions within each of three

successive estrous cycles from the study of

Adamiak *et al.* [30]. Heifers were moderately 0.0

fat at the beginning of the experimental

period and were offered a high-calorie diet at

-0.1

a level equivalent to twice their metabolizable

energy requirements for maintenance.

-0.2

Oocytes were matured, fertilized, and

insulin

cultured to the blastocyst stage in vitro. Mean

inseminated

-0.3

plasma insulin concentration for these

of

/ml

animals was 48 IU/ml.

µIU -0.4

per

-0.5

$P < 0.001$

Blastocysts

-0.6

-0.7

4

5

6

7

8

9

10

11

12

Weeks from when dietary treatments were introduced

or biochemical hyperandrogenism, and/or polycys—

weeks, and systolic blood pressure was elevated in both tic ovaries [33]. It is also frequently associated with sexes at 21 weeks. A feature of this study and that insulin resistance and hyperinsulinemia. Oocytes from of Minge *et al.* [31], however, was that fertilization obese and hyperinsulinemic PCOS patients frequently occurred in vivo while dams were still on their exper-fail to fertilize, and those that do often fail to imental treatments, so that dietary effects on fertiliza-implant, even following surrogate embryo transfer tion and related-related events (discussed later) cannot [34]. Microarray analysis of metaphase II oocytes from be ruled out.

normal ovulatory women and women with PCOS

identified a subset of differentially expressed genes **Summary 17.1**

associated with chromosome alignment and segrega—

r Although a number of animal studies indicate

tion during meiosis, and genes containing putative

that ovarian stimulation can impair egg quality,

androgen receptor and PPAR gamma binding sites

postfertilization development, and pregnancy out-

[35]. These observations may help explain impaired come, there is a lack of compelling evidence to oocyte quality and pregnancy establishment in PCOS

indicate that this is the case in human assisted

subjects, but longer term developmental consequences reproduction, where factors such as subfertil—

are not known.

ity, maternal age, and embryo culture confound

In fact, few studies have specifically assessed the

interpretation.

long-term developmental consequences of maternal

r Overweight women, excluding those with PCOS,

diet on oocyte quality. Most, including studies at the face a lower likelihood of pregnancy establishment

author’s laboratory, have had protracted treatment

and an increased risk of miscarriage following

periods that extended into early pregnancy [36]. One IVF.

r

study, however, assessed the effects of maternal low-Although recent animal studies have demonstrated significant improvements in oocyte quality

protein diet (LPD; 9% casein) restricted to one ovu—

following the treatment of obese egg donors with

latory cycle before natural conception in mice [37].

insulin-sensitizing agents, their efficacy in assisting The authors observed no effects on pregnancy estab—

with ovulation induction and pregnancy establish—

lishment or outcome but reported increased anxiety—

ment in PCOS women is variable, and so routine

related behavior in offspring. Furthermore, male mice use is currently not recommended.

exhibited elevated systolic blood pressure at 9 and 15

activated embryos that developed to the blastocyst

The metabolite composition of follicular fluid and

stage had a reduced inner-cell mass and a higher num-granulosa cells, normally discarded at the time of ber of TUNEL-positive cells. Microarray analysis iden-egg recovery in IVF cycles, can be used to predict postfertilization development.

tified in excess of 800 genes that were differentially expressed between the treatments. Significantly, cell cycle–related and growth arrest genes, together with apoptosis-related genes, appeared to be overexpressed **Fertilization**

in the activated-activated embryos.

Calcium oscillations around fertilization are

There is sparse information concerning the effects of known to have longer-term

consequences on

maternal diet on the processes involved in fertiliza-development, influencing implantation in rabbit tion, although it is now apparent that events during parthenogenotes [42] and, more recently, term devel-this period can have a profound effect on long-term opment following fertilization in the mouse [43]. In development. The sperm in mammals does not appear the latter study, Ca2+ oscillations were either inhibited to provide the egg activation signal by the conventional or overridden and experimentally increased following interaction with a receptor linked to the production the first few endogenous oscillations induced by the of the Ca2+ releasing messenger inositol triphosphate fertilizing sperm. In either case, development to the (IP3); rather, it uses a more direct route by introduc-blastocyst stage was unaffected, but development to ing a soluble signaling molecule that triggers endoge-term was compromised. When the natural pattern of nous Ca2+ release. Upon membrane fusion, a novel

signaling was prematurely interrupted, implantation

sperm-specific form of phospholipase C, referred to as rate was reduced. In contrast, when Ca2+ oscillations PLC (zeta), is released into the ooplasm, and this trig-around fertilization were experimentally increased, gers endogenous Ca2+ oscillations by increasing intra-implantation rates were not affected, but resorption cellular concentrations of IP3 [38]. This mechanism rates increased. Furthermore, there appeared to be appears to be highly conserved across species. Indeed, long-term effects on weight variation in offspring

the injection of primate PLC into mouse eggs has

derived from this latter treatment group. Microarray been shown to induce Ca2+ oscillations and to activate analysis of gene expression in blastocysts revealed

development [39].

that approximately 20% of transcripts were misregulated when too few oscillations occurred. In

contrast, only approximately 3% of transcripts were

Of particular interest to the current thesis are the misregulated when Ca2+ oscillations were increased.

recent observations in mice that perturbations to Ca2+

In the former case, genes involved in transcription

oscillatory signaling during the first few hours follow-regulation, mRNA processing, and cell adhesion were ing insemination can have long-term effects on devel-preferentially misexpressed, whereas in the latter case, opment. It has been known for some time that the pat-genes involved in metabolism were dysregulated.

tern of Ca2+ transients during parthenogenetic acti—

The mechanisms of action of Ca2+ oscillations on

vation of rabbit eggs can influence the proportion of gene expression, however, are not understood, so that embryos that reach the compacted morula or blas—

it is currently not possible to gain further insights tocyst stage [40]. A recent study in mice, however, into these differential effects. It is also not known used a number of recognized agents, including the

what effects maternal nutrition or media metabolite

protein synthesis inhibitor cycloheximide, which does composition may have on these processes. However,

not rely on the actions of Ca2+, to parthenogeneti—

Ca2+ oscillations are influenced by oxidative stress cally activate eggs [41]. These authors also conducted through the generation of reactive oxygen species a microarray analysis of gene expression in eight-

(ROS) from the mitochondria in aged oocytes [44].

cell embryos. A greater proportion of embryos that

The culture of mouse embryos in the presence

underwent Ca2+ oscillations or a single Ca2+ increase of both n-3 and n-6 polyunsaturated fatty acids

developed to the blastocyst stage than those from the (PUFAs) increased lipid peroxidation and intracel—

cycloheximide-activated group, which experienced no

lular ROS, and decreased embryo development, an

Ca2+ oscillations. Furthermore, those cycloheximide—

effect attenuated by the addition of antioxidants [45].

171

Section 3: Specialized requirements More recently, ROS production was increased and

colony-stimulating factor (GM-CSF), which has been

intracellular Ca2+ homeostasis perturbed in mature

shown to promote preimplantation development of 8—

oocytes from mice offered n-3 PUFA-enriched diets,

cell mouse embryos in vitro by increasing the num—

resulting in a reduced proportion of cleaved zygotes ber of viable blastomeres and by enhancing glucose

[46]. Once again, the precise mechanisms of action uptake [52]. Embryotrophic effects of GM-CSF in vitro of these dietary effects are not understood, and have been reported in other species, including the cow long-term developmental consequences remain to be

[53] and human [54]. Significantly, this latter group established.

found that GM-CSF added to mouse embryo cul—

These observations, however, may have profound

ture media alleviated at least some of the effects of implications for the safety of assisted reproductive in vitro culture on fetal and postnatal development

techniques such as intracytoplasmic sperm injection

[55]. The inclusion of GM-CSF in media used to cul-

(ICSI) and the formulation of culture media for IVF.

ture two-cell mouse embryos to the blastocyst stage

The current consensus, based on ICSI outcome stud—

before transfer led to increased litter sizes, improve-ies in humans, is that there is a significant, albeit low, ments in near-term fetal weights, and a normaliza—

increased risk of preterm delivery, low birth weights, tion of postweaning growth relative to offspring from and perinatal mortality in both single and multiple

nontreated in vitro cultured embryos. GM-CSF was

births, although it is difficult to isolate completely unable, however, to overcome the increased levels

the effects of ICSI from the recognized risk factors of obesity, particularly central obesity, observed in of maternal age and infertility [25]. ICSI not only adult offspring from cultured embryos, indicating that bypasses membrane fusion of gametes but leads to

more than one mechanistic pathway is involved in this the delivery of a membrane-intact sperm head, which

pathology.

could impair the release of sperm factor. Indeed, ICSI-generated zygotes in the mouse cleaved at a slower rate, had lower cell numbers, and had lower hatching

Summary 17.2

r

rates [47]. This was associated with shorter duration Intercourse, specifically exposure to semen, Ca^{2+} oscillations. Curiously, ICSI is much less success- around the time of embryo transfer can increase ful in the bovine. The problem here appears to lie in the likelihood of pregnancy establishment in

humans.

the initiation of Ca^{2+} oscillations following injection.

r Be wary of natural conception, which can arise if

For reasons that remain unclear, the majority of bovine oocytes not collected during follicular aspiration

oocytes appear unable to mount such oscillations and become fertilized, because this can lead to multi—

subsequently fail to cleave [48].

ple pregnancies.

r Prolonged exposure to semen and/or seminal

Intercourse and seminal plasma

plasma from a single source, a feature of monog—

amous relationships, can further induce functional

Studies across a broad range of mammalian species

tolerance to male antigens, enhancing placental—

indicate that semen introduced to the female repro—

fetal development during late gestation and mini—

ductive tract elicits a cascade of molecular and cellu-mizing the risk of preeclampsia.

r

lar changes that can promote conception and improve

Although the underlying mechanisms of these

pregnancy outcome [49, 50]. Seminal plasma induces effects are not fully understood, current models in the synthesis and release of embryotrophic cytokines the mouse are investigating the effects of TGF1,

which can induce a state of systemic functional tol—

and chemokines from estrogen-primed oviductal and

erance to paternal major histocompatibility com—

uterine epithelial cells, which can interact with the plex class I antigens.

cleavage-stage embryo before implantation. Trans—

forming growth factor beta (in particular, TGF1) is a cytokine present in abundance in seminal plasma

and is one of the principal factors responsible for ini-Preimplantation development tiating this inflammatory response [51]. One of the Preimplantation development can also be character-key pro-inflammatory cytokines for which expression ized by three major transitions. The first transition is upregulated by TGF1 is granulocyte-macrophage

concerns activation of the embryonic genome, the

 timing of which varies between species [56]. The sec-mouse, where the paternally derived genome, which is ond is compaction, where adhesive junctions form

packaged densely with protamines, is actively (in the between individual blastomeres to create the first

absence of DNA replication) demethylated during the

transporting epithelium [57]. The third transition is first cell cycle [63, 64]. The

maternal genome, in con-blastocyst formation, where the outermost cells of trast, is passively demethylated during the first few cell the embryo differentiate to form the trophectoderm,

cycles. Approximately equivalent levels of hypomethy-which gives rise to extraembryonic tissue. These events lation are attained by each genome around the 16—

occur during a comparatively short period of time

cell stage, after which the combined genomes undergo (Ↄ 7 days in most mammalian species) where, curi—

de novo methylation in a cell lineage specific manner.

ously, embryo metabolism operates at a relatively low Although similar patterns of global DNA demethyla—

level [58]. However, although nutrient demands of the tion of the paternal genome have been observed in the embryo during this period are quantitatively small,

rat, cow, and human zygote, this has not been observed they are, nevertheless, qualitatively specific and reflect in either the rabbit or sheep zygote [65]. Although the the changing needs of the embryo in response to nutri-functional significance of these species-related different supply during its migration from the oviduct to the ences in DNA methylation is unclear, they may partly uterine lumen [59].

reflect preexisting levels of methylation in the male pronucleus at the time of syngamy, which are compar—

Transcriptional activity and DNA

atively low in the sheep [66], or differential expression patterns of DNA methyltransferases in the oocyte and methylation

preimplantation embryo [67, 68].

Transcript profiling during mouse embryo develop—

A dramatic increase in biosynthesis follows com—

ment has characterized the three transitional peri—

paction (typically around 8 to 16 cells [59]). In the ods referred to earlier [60]. The first of these spans mouse, this is immediately preceded by the activation the period from oocyte maturation to the onset of

of a series of related genes involved in ribosome bio-embryonic transcription, during which time more genesis, and protein and phospholipid synthesis [60].

than 90% of maternal RNA is destroyed. A large sub—

In contrast, a smaller set of genes, mostly involved in set of these genes is involved in cell-to-cell communi-metabolism, are turned on in the blastocyst. On an cation, signal transduction, and cell adhesion required embryo basis, the generation of ATP increases expo—

to maintain bidirectional communication between the

nentially following compaction and blastocele forma—

oocyte and surrounding cumulus. The rapid demise

tion although, at a cellular level, oxidative and gly-of these pathways is hypothesized to “insulate” the colytic activities alter little [59]. The -oxidation of embryo during this transitional period from extra-fatty acids by apposing mitochondria is believed to cellular signals to maintain its totipotent state. Inter-generate much of the water and at least some of the estingly, metabolic activity during these early cleav-energy necessary for blastocele formation.

age stages (i.e. to approximately the eight-cell stage) is comparatively low in terms of adenosine triphosphate (ATP) production and de novo protein synthe—

Embryo culture

sis [59], and subsequent embryo viability is inversely Early embryo culture media formulations were related to the level of metabolic activity during this adapted from those used for cell culture, and sub—

period [61]. Indeed, the early embryo would appear to sequent modifications were largely empirical. These exert a high degree of autonomy and relies heavily on media were often complex with many components

utilizing endogenous reserves of protein and energy, included at nonphysiological levels [69]. Serum was mostly in the form of triglycerides [62]. These observa-commonly included, often with somatic support cells tions, however, belie the incredible turmoil that occurs to promote embryo development beyond the cleavage

upon sperm-egg union and egg activation (discussed

stage. Indeed, interest in the use of co-culture systems earlier), pro-nuclear formation, DNA replication, and for human embryo culture persists [70]. Most labora-chromatin modifications.

tories, however, have abandoned such systems in favor Epigenetic programming during this early period

of more chemically defined and “sequential” media

of embryo development has been best studied in the

formulations that have contributed to the significant **173**

Section 3: Specialized requirements improvement in postfertilization development and

[77]. It is noteworthy, however, that extended periods clinical pregnancies observed over the past decade of culture to the blastocyst stage are routinely prac-following assisted reproduction (ART) [71].

ticed in ruminant embryo production, so that the rela-The incentive to remove both serum and somatic tively high incidence of imprinting anomalies in these support cells from culture arose from reports that

species may be a feature of extended culture following emerged during the 1990s of aberrant in utero devel—

IVM and/or ovarian stimulation.

opment, leading to large offspring, in both cattle and sheep following the transfer of embryos that had

Maternal diet and embryo quality

been cultured in the presence of these components

[11]. Referred to as the “large offspring syndrome”

Evidence that subtle alterations to the in vivo envi-

(LOS), characteristic features of this phenomenon,

ronment of the early cleavage-stage embryo can lead

other than its sporadic occurrence, include in utero to long-term effects on fetal development came from

overgrowth and perturbed growth allometry, con—

some of our earlier studies into LOS where we tem—

genital anomalies involving the central nervous sys—

porarily (for 3 days) exposed Day 3 sheep embryos

tem, gastrointestinal tract, and cardiovascular systo an advanced uterine environment. Although there

tem, polyhydramnios, and allantoic aplasia [72, 73].

was no effect on pregnancy establishment and no gross Often newborns from in vitro–produced ruminant

effect fetal mass [78], myogenic regulatory pathways embryos experience greater difficulties in adjusting were altered. These included a temporal shift in the to extrauterine life. Many exhibit aberrant metabolic expression of Myf5 protein (a member of the MyoD

activity including hypothyroidism, hypoxemia, hypo—

gene family responsible for myoblast proliferation), glycemia, hyperinsulinemia, and metabolic acidosis.

leading to an increase in muscle fiber number and the Importantly, a number of features of this syndrome are ratio of secondary to primary muscle fibers [79].

strikingly similar to several naturally occurring over-One of the first studies to show that maternal diet growth syndromes in humans, most notably Beckwith—

during the preimplantation period can have a long—

Wiedemann syndrome (BWS), which is associated

term effect on development and offspring health was

with abnormalities in an imprinted cluster of genes

conducted in the rat. A maternal LPD (described ear—

on chromosome 11 (11p15.5) [11]. In our studies with lier) given to dams from Day 0 to 4.25 altered post-sheep, exposure to serum throughout the 5-day period natal growth and hypertension in male pups at 12

of embryo culture or during the first 3 days of cul—

weeks of age [80]. Subsequent follow-up studies by ture had the most dramatic effect on ovine fetal devel-this group also pointed to sex-specific programming opment [74]. We had earlier demonstrated that these of imprinted gene expression as a possible contribu-effects were associated with a loss of imprinting (loss of tory factor in this phenomenon [81]. Curiously, the methylation on the second intron differentially methy-expression of both H19 and Igf2 was reduced in only lated region) of the normally active maternal allele male embryos and fetal tissues. It would appear that in of the type 2 insulin-like growth factor receptor gene a nutrient-restricted (i.e. LPD) environment, the early (Igf2R), which resulted in a significant reduction in its embryo is capable of activating a series of as yet poorly expression in all affected tissues within LOS fetuses defined mechanisms that attempt to normalize con-

[75]. Similar imprinting anomalies have since been ceptus growth and postnatal fitness but may predis-reported in mice [76], and, of most concern, in humans

pose offspring to certain adult diseases [82].

following ART [77].

The absolute risk of inducing imprinting disorders

Effect of B vitamins in the

in human ART pregnancies, however, would appear to

be small. For example, analysis of data from several periconceptional diet

studies indicates that the incidence of BWS following Given that sweeping epigenetic modifications to DNA

ART may increase to 1 in 4500 relative to the natu—

and related proteins take place during the peri—

ral incidence of imprinting anomalies associated with conceptional period (discussed earlier), we recently BWS of 1 in 28 000. To date it has not been possible to tested the hypothesis that a restricted supply of

attribute this phenomenon to any specific component

specific B vitamins (i.e. vitamin B12 and folate)

of culture media, to manipulative procedures such as and sulphur amino acids (in particular, methionine)

ICSI or, indeed, to the type of infertility in humans from the diet of adult female sheep, from 8 weeks

 preceding until 6 days following conception, would

cess of development accurately under such conditions lead to epigenetic modifications to DNA methylation

may be compromised. Thus far, the consequences for

and affect adult health in offspring [83]. The duration human development and health either have been too of exposure to “methyl-deficient” diets ensured that subtle or have occurred too infrequently to be ade—

the critical periods of DNA methylation programming

quately determined. They are also confounded by fac—

that occur in both the oocyte (Figure 17.1) and embryo tors such as underlying infertility and maternal age.

were incorporated. The transfer of Day 6 embryos to

The longer-term effects of maternal diet around the

normally fed surrogates further ensured that the tim-time of conception have, until comparatively recently, ing of dietary treatments was limited specifically to the been poorly investigated. Animal studies once again, periods of oocyte growth and early postfertilization however, point to very subtle programming effects that development. We observed no effects on pregnancy

may not affect fertility and pregnancy outcome but that establishment or birth weight, but adult offspring were may manifest as disease in adult life.

heavier and fatter, elicited altered immune responses to antigenic challenge, were insulin resistant, and had elevated blood pressure. Curiously, these effects were

Summary 17.3

most obvious in male offspring. Furthermore, the

r Given the relatively high incidence of genomic

altered methylation status of 4% of 1400 CpG islands imprinting-related anomalies in animal studies

examined by restriction landmark genome scanning

following ovarian stimulation and/or following

in the fetal liver revealed compelling evidence of a extended periods of gamete/embryo culture, the

widespread epigenetic mechanism associated with this widespread uptake of procedures such as oocyte

nutritionally programmed effect. These findings in a in vitro maturation and blastocyst culture should

large outbred species, in which pre-and postnatal

proceed with caution.

r

development and physiological approximates that of

Noninvasive

assessments

of

preimplantation

humans, have profound implications for nutritional

embryo development to the blastocyst stage

in vitro have developed to usefully combine

advice offered to intending mothers, where the mes—

morphological, kinetic, and metabolic criteria.

sage to date has focused on the protective effects of folic Such developments have the potential to further

acid around the time of conception against the devel-improve predictions of pregnancy outcome, opment of neural tube defects.

in which more simple measures of embryo

metabolism have already been found to correlate

Conclusions

with clinical pregnancy rates following embryo

transfer in humans.

The major changes in transcriptional activity and the r In addition to the well-documented protective

extent of epigenetic reprogramming that take place

effects of folic acid against the development of

around the time of conception make it a particularly neural tube defects, maternal B vitamin status dur—

sensitive period to environmental influences, including the periconceptional period can have a major ing maternal diet. The success of ART has, to a large impact on fertility, pregnancy establishment, and

extent, relied on the remarkable tolerance of mam—

term delivery and can determine pregnancy out—

malian gametes and cleavage-stage embryos to phys—

come in clinical IVF cycles. New data now indicate that there may also be more subtle, long—

ical manipulations and alterations to their chemical term developmental consequences of deficiencies

environment. There is emerging evidence from studies in these vitamins around the time of conception

in both animals and humans, however, that the ability that determine offspring adult health.

of these “germ cells” to recapitulate the normal pro-175

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Section 3

Specialized requirements

Chapter

18**Nutrition,environment,andepigenetics** Ian M. Morison and Wolf Reik

Key messages

boring cells contribute to the gene activity (expression) of a cell, but gene expression is also regulated by **Epigenetics.** In this chapter, we refer to epigenetic long-term modifications to the DNA and chromatin

modifications of the genome, which include deoxyri—

itself, referred to as epigenetic modifications. Through bonucleic acid (DNA) methylation and histone mod—

the effects of DNA methylation, together with other

ifications. These modifications result in structural epigenetic modifications, genes can be permanently

changes to chromosomal regions, resulting in altered silenced. As development and differentiation proceed, activity states [1]. In other words, epigenetic modifi-differentiated cells accumulate epigenetic marks that cations have the potential to cause mitotically and/or differ from those of pluripotent cells and distinguish

meiotically heritable changes in gene function that are cells of different lineages.

not attributable to changes in DNA sequence.

Epigenetic regulation has a well-defined role in

Maternal dietary manipulation. Changes in DNA the normal physiological events of X chromosome

methylation and phenotype that occur after maternal

inactivation, genomic imprinting (discussed later), the dietary manipulations in mutant Agouti and Axin1

maintenance of genomic integrity, and the silencing of mouse models provide convincing evidence for the

retrotransposon elements. Its role in defining cell fate role of epigenetics in shaping adult phenotypes. It is and lineage determination during organ development

plausible that similar changes in human maternal diet is being documented in increasing detail. An impor—

will affect the epigenotype of children, thereby affect-tant recent development is the recognition of plastic-ing their phenotype including their lifelong suscepti-ity within the epigenetic modifications of the genome, bility to disease.

and with it, the potential for the epigenome to be mod-Environmental manipulation. The use of assisted ified by environmental factors, including the nutri—

reproductive technologies in humans and animals is

tional state of the fetus.

associated with altered epigenetic states in a small Environmental factors can modify epigenetic pro—

minority of children and in a substantial proportion gramming at many stages of

development, and in so

of animals. The identification of factors that contribute doing epigenetics provides an organism with a mech—

to these epigenetic changes has important implications anism by which it might “remember” its past expo—

for reproductive technologies and also for the role of sures. For example, it is now clear that the environthe environment in epigenetic plasticity.

ment of a cultured preimplantation embryo can affect its epigenetic modifications. In utero, maternal dietary

Introduction

manipulation is clearly associated with changes in

The growth and physiological function of cells and

epigenetically controlled phenotypes in mouse mod—

organs within a fetus, child, and adult rely on approels such as the agoutivy mouse. During the postna—

priate switching and regulation of approximately

tal period, maternal behavior can permanently mod—

20 000 genes that make up the human genome. During

ify the behavior of offspring through mechanisms that development, pluripotent embryonic and trophoblas—

might include epigenetic modifications.

tic cells differentiate into cells and organs with specific The focus of this chapter is to highlight develop—

functions and heritable memories of their identities. A mental opportunities for

nutritionally induced vari—

cell’s identity is controlled by many factors. Endocrine ation within the epigenotype (Figure 18.1). In addi-signalling, physiological cues, and signals from neigh-tion, normal programmed, epigenetic modifications Developmental

Figure 18.1 Epigenetic modification,

influenced by nutritional and environmental

environment

exposures, is superimposed on the genome and

contributes to long-term regulation of gene

Long-term

expression. Secondary epigenetic modifications,

changes in gene

Secondary

resulting from changes in gene expression, can

Genotype

Epigenotype

expression.

epigenetic

be difficult to distinguish from primary

Adult

modifications

epigenetic changes.

phenotype

Nutrition

are critical for nutrient supply to the fetus. This aspect transposed retroelements, given the need to mainis discussed with reference in particular to the role of tain genomic integrity by preventing the transcrip—

imprinted genes in placental function.

tion of mutagenic retrotransposons [3]. Methylation is also required for preservation of genome stability **Epigenetic modifications**

through its effects on pericentromeric and other repetitive DNA [4].

DNA methylation

Methylation that is associated with gene promoters is likely to be of physiological relevance because DNA methylation and histone protein modifications

it has the potential to alter gene expression and thus interact to provide a stable epigenetic mechanism by a cell's phenotype. The promoters and first exon of

which genes are made accessible for activation or ren-approximately 70% of genes contain regions that have dered inactive. DNA methylation changes the chemi—

a high density of CpGs often referred to as CpG

cal structure of the base within the double helix itself, islands [5]. These CpG-rich promoter regions remain whereas histones affect the structure of the nucleo-unmethylated in most genes, but in a minority, they some, and thereby the openness of the chromatin.

acquire methylation, often in a tissue-specific man—

Interactions between DNA methylation and his—

ner [6]. The consequence is gene silencing, which is tone modifications are being progressively elucidated.

often irreversible. The best-studied examples of gene In vertebrates, DNA methylation almost exclusively

promoter methylation involve genes on the inacti—

affects cytosine nucleotides in the context of cyto—

vated X chromosome and imprinted genes. Imprinted

sine guanine dinucleotides (CpGs) (the “p” denotes

genes comprise a group of approximately 100 genes

the intervening phosphate group). Throughout the

for which gene expression is dependent on the parent genome, the majority of CpG-associated cytosines are from which the allele was inherited [7]. The silencing methylated, gene promoter regions being the excep-or activation of one parental copy of imprinted genes tion in that they usually remain unmethylated [2].

is mediated by methylation marks that are applied to Because every CpG dinucleotide is inevitably associ—

imprint control regions during gametogenesis. Of the ated with a reciprocal CpG on the opposite strand, the imprinted genes, approximately 20 are directly con—

cytosines on both strands can be, and are, reciprocally trolled by a differentially methylated region overlap-methylated. This reciprocal methylation provides the ping with their promoter. The parental allele that is basis for the heritability of the epigenetic modification methylated is silent, whereas the unmethylated allele to daughter cells, in that, following DNA replication, is expressed. The remaining imprinted genes are con—

the hemimethylated CpG provides the template for the trolled through secondary modifications that do not

maintenance DNA methyltransferase, DNMT1, which

usually involve methylation.

restores the original pattern of DNA methylation to the Although anticipated for many years [8], a role for newly replicated strand of DNA.

methylation in cell differentiation has only recently been confirmed. For some genes, early steps of

Roles of DNA methylation

differentiation involve tissue-specific methylation to DNA methylation has multiple roles in regulating and maintain silencing permanently. For example, Oct4

maintaining the integrity of the genome. Its role may and Nanog, genes critically important for maintain-

have originated as a mechanism to silence newly retro-ing pluripotency in embryonic stem cells, become **Section 3: Specialized requirements** Figure 18.2 DNA methylation and

histone modifications together make up

the best-studied epigenetic modifications.

The presence of DNA methylation (stars)

attracts DNA binding proteins, which in

Methyl binding

turn recruit proteins that induce repressive

protein

histone modifications (stop signs) and lead

yl binding

to compact chromatin with repressed gene

Meth protein

transcription.

yl binding

protein

Meth

STOP

STOP

STOP

STOP

methylated in differentiated tissues to prevent inap-In contrast, lysine methylation states may be associ-propriate pluripotency [9, 10]. Increasing numbers of ated with long-term heritable states of gene activity developmental epigenetic switches are being identi-

[14]. Specific histone modifications can be recognized fied [11], but key questions remain. How many devel-by specific “reader” proteins (such as HP1 for H3K9

opmental epigenetic switches are plastic, that is, how methylation), which in turn can be associated with

many genes can be influenced by extrinsic factors?

transcriptional repressors or activators [14].

During which phases of development can stable long—

Interaction between DNA methylation and his—

lasting epigenetic modifications be made? Are these

tone modification is bidirectional [15] (Figure 18.2).

switches binary (on or off), or variable as in a rheostat?

For example, DNA methyltransferase enzymes are

recruited to complexes associated with the repressive Histone modifications

histone 3 lysine 9 methylation. Conversely, methylated DNA can be bound by DNA methyl-binding

DNA is wrapped around histones to form nucleo—

proteins, which in turn recruit chromatin remod—

somes. Each nucleosome comprises two of each of the

elling co-repressor complexes. MBD1, for example,

core histones H2A, H2B, H3, and H4 together with

associates with the histone methyltransferase SetDB1, approximately 146 bp of DNA wrapped around the his—

thereby coupling DNA methylation to repressive histone octamer.

tone methylation. Although most of the examples pro—

The histones are modified by a plethora of post—

vided here relate to observations of DNA methylation, translational protein modifications, predominantly

it should be noted that commensurate alterations of

within the amino terminal tails that project externally the neighboring histones might also be occurring.

from the nucleosome [12]. These modifications determine the structure and

compaction of the chromatin and are associated with the level of transcriptional activity. For example, methylation of specific lysines **Cycles of epigenetic modification** (H3 lysine 4 and H3 lysine 36) is often associated with The cycle of mammalian life entails a progression from active genes, whereas methylation of other lysines is the totipotency of an early embryo, through to the

associated with gene repression (H3 lysine 9, H3 lysine loss of multipotency associated with differentiation of 27, and H4 lysine 20). The heritability and stability of somatic and extraembryonic tissues, but then repro—

the histone modifications remain poorly understood

gramming of the germ cells to provide a return to

[13]. Histone acetylation is a transient modification, totipotency in the next generation. This cycle is accom-182

observed in genes that are being actively transcribed.

panied by series of epigenetic events, each of which **Chapter 18: Nutrition, environment, and epigenetics** provides a potential opportunity for natural or patho-blastocyst transition, the methylation of the genome is logical variation.

restored, progressively to adult levels. It is interesting To summarize these epigenetic steps, we choose

to note that average methylation of the trophectoderm an arbitrary beginning point of the epigenetic cycle, DNA is lower than that in the inner cell mass, indicat-that is, the fusion of the gametes at fertilization.

ing that different tissues can modulate their genomic The oocytes and sperm carry epigenetic marks that

methylation. Of note, the kinetics of demethylation

reflect their tissue type and their parental origin, and remethylation vary between different mammalian

but within hours of fertilization, a wave of epige—

species [17].

netic reprogramming occurs. This reprogramming

The dynamic and massive changes in methylation

includes genomewide DNA demethylation in the

during the first few cell divisions and days of life zygote, together with changes in histone modifica—

have multiple implications for human development.

tions [16]. The wave of DNA demethylation presum-First, the opportunities for generalized perturbation ably exists to erase epigenetic modifications that were or manipulation of epigenetic programming may be at

specifically required for germ cell and gamete devel-their greatest at this stage. More specifically, if the effi-opment. Within a few cell divisions, however, represciency of either, or both, demethylation and remethysive epigenetic modifications begin to be applied to lation is affected by the environment, through the

the early embryo. These epigenetic changes include

availability of methyl donors or by other features of consolidation of the parental imprints, X chromo—

maternal nutritional state, then there is the opportu-some inactivation in females, inactivation of retronity for epigenetic variation in the offspring. Second, transposons, and the early stages of lineage commit—

in the assisted reproductive technologies (ART), it is ment and differentiation. As development proceeds in this stage of development that occurs in vitro in arti-the embryo and newborn, there are ongoing modifica—

ficial media. Third, if epigenetic modifications applied tions to the epigenome, some of which may be influ—

to the gametes (discussed later) are to have an effect enced by the environment

of the developing animal.

on a child, those modifications must survive the epiThe germ cells of the developing fetus begin a dis—

genetic erasure in the zygote.

tinct branch of the cycle, wherein the epigenetic marks of the embryo are erased, wiping the slate clean for the new generation. The developing germ cells and

Diet-associated hypomethylation in sheep

gametes then acquire new epigenetic marks including

The methylation of cytosine requires donation of a

the imprinting marks that signal the parent-of-origin-methyl group by S-adenosyl methionine (SAM). If the specific gene expression and the repressive modifica-dynamics of demethylation and remethylation in the tions required to silence (retro)transposons [3].

zygote are affected by the availability of methyl donors, Each of these steps has the potential to be affected it follows that SAM levels might influence the overall during normal and aberrant development. For some of

methylation state of an organism. SAM provides

these modification steps, there is evidence of develop-methyl groups not only for DNA but also for protein mental plasticity that might allow for environmentally and lipid methylation, and its levels are affected by or nutritionally induced modification of the epigenetic changes in the B12 and folate pathways (Figure 18.3).

program, and consequently the phenotype.

It must be remembered, however, that the functions

of folate and other constituents of the pathway extend **Epigenetics of the early embryo**

well beyond the supply of methyl donors.

To address the role of vitamin B12, folate, and

methionine in periconceptual sheep development,

Epigenetic programming in the zygote

Sinclair and colleagues [18] induced “methyl-The process of fertilization sets in motion a massive deficiency” in maternal sheep and, following transfer reprogramming of the epigenome. In the early mouse

of the embryos to recipient ewes, demonstrated long—

embryo, the parental genomes undergo extensive

term epigenetic and phenotypic changes in adult off—

demethylation, the paternal genome being actively

spring. Methyl deficiency was achieved by reducing the demethylated within a few hours, whereas the mater—

dietary cobalt and sulphur levels, thus diminishing the nal genome is progressively demethylated up to the

capacity of the rumen organisms to synthesize sulphur **183**

morula stage. From the time of the late morula–early amino acids (including methionine) and vitamin B12.

Section 3: Specialized requirements dTMP

Figure 18.3 Simplified overview of folate

DNA synthesis

metabolism. Dietary factors (folate, vitamin B12,

choline, and betaine) that might affect

methylation are shown. DHF, dihydrofolate; THF,

tetrahydrofolate; SAM, S-adenosylmethionine;

SAH, S-adenosylhomocysteine.

Folate

DHF

10-formyl THF

5,10-methylene THF

THF

5-methyl THF

B12

Betaine

Homocysteine

Methionine

Choline

SAH

SAM

CH3

Substrates (DNA,

Methylated substrates

RNA, proteins, lipids)

Although the levels of plasma vitamin B12, folate,

manipulation of the epigenotype. The Avy mutation

and methionine in the donor ewes remained within

resulted from insertion of an intracisternal A-particle normal physiological ranges, they were significantly (IAP) retrotransposon in the promoter of the agouti

reduced compared with control animals. “Deficient”

gene. When the IAP is active, the coat color is abnor-and control Day 6 blastocyst embryos were then transmal (yellow), and the mice become obese and develop ferred to normally fed surrogate ewes. As adults, male tumors, but when the IAP element is silenced by

offspring of treated ewes showed increased weight

methylation, the phenotype is normal. In any one litand were fatter, had impaired insulin sensitivity, and ter, the mice can show the full range of coat colors had higher blood pressure. Putative epigenetic modi—

that vary from yellow (unmethylated), through mot—

fications, most of which involved reduced DNA met—

tled, to normal (so called pseudoagouti; fully methy-hylation, appeared to affect 4% of the genes studied.

lated). This intra-and intermouse variation in coat This study indicates that nutritional modification

color indicates the occurrence of epigenetic variability, of early embryos can have lasting phenotypic effects, the level of which is set early in embryogenesis before notably affecting physiological functions that are rele-lineage-specific tissue differentiation has occurred vant to the detrimental effects of famine and low birth [19].

weight in humans (discussed later). Questions of cause The key point about the Avy mouse model is

and effect remain. What is the role of altered DNA

that a supplemented maternal diet (enriched with

methylation? Does it constitute the heritable mem—

methyl donors: folate [3-fold enrichment compared

ory that brings about adverse phenotypic changes in

with NIH-31 diet], vitamin B [12] [20-fold], betaine, adulthood, or is it simply a consequence of altered cell and choline [3-fold]) shifts the average coat color of metabolism?

the offspring toward normal [20] and that this normalization is associated with an increase in methylation Diet-induced hypermethylation

of the IAP retrotransposon [21]. It has been proposed that the altered maternal diet increases the availabil-in the agoutivy mouse ity of methyl donors, which then modulate the epigeThe agouti viable yellow (Avy) mouse model provides

netic modifications of the IAP promoter at the mutant

another useful example of the potential for dietary

agouti gene.

Chapter 18: Nutrition, environment, and epigenetics The observations on the methyl-deficient sheep

etrance of the mutation is inversely correlated with and the Avy mice raise profound questions for the

the degree of methylation of the IAP [25]. As for the role of diet in human epigenetic programming. How Avy mouse, methylation levels are concordant across

many genes might be affected by the changes in the

multiple tissues (liver, kidney, brain), reflecting sim-apparent abundance of methyl donors? Given that ilar modifications in each of the different germ lay-

pseudoagouti Avy mice are leaner and longer lived ers of the early embryo. Furthermore, modification

than agouti Avy mice [20, 22], it might be predicted of mothers' diet, by addition of folate, vitamin B12, that a methyl-supplemented diet would have beneficial choline, and betaine, resulted in a substantial reduc-effects, such as reducing the obesity and tumor predis-tion in the severity of the kinked-tail phenotype, which position of these mice. In contrast, human birth weight was associated with increased methylation of the IAP

is positively correlated with maternal folate status [23].

element [26].

Obviously the long-term effects and mechanisms of

action of methyl-donor supplementation need to be

determined.

Epigenetic variation in human

Can the lessons from nutritional manipulation

be generalized, or are changes restricted to genes

AXIN1 methylation

that contain IAP and related elements? Would it be

A fascinating human parallel with the Axin1Fu mouse

expected that a mother who has a diet rich in folate might be provided by the human congenital disorder

and other methyl donors would have hypermethylated

caudal duplication anomaly in which there is dupli—

offspring compared with the hypomethylated offspring cation of the distal spine and pelvic organs. In a pair of folate-deficient mothers? What is the mechanism

by of monozygotic twins discordant for the caudal dupli-which maternal diet modifies the epigenome of the off-cation anomaly, the affected twin was found to have spring?

significantly more AXIN1 promoter methylation than

Notably the administration of genistein, a soy—

the unaffected twin and controls [27], suggesting that derived phyto-estrogen, to mice similarly increases the silencing of the AXIN1 gene played a causative role

average level of methylation of the Avy IAP, altering and that nongenetic factors can influence the level of coat color and protecting against later obesity [24].

methylation. Furthermore, in the control population, Conversely, the estrogenic xenobiotic chemical bisphe-there was variation in the degree of AXIN1 methyla —

nol A (BPA) that is used in the manufacture of polycar-tion, thus establishing AXIN1 as a candidate gene for bonate plastic and epoxy resins was shown to reduce

environmentally induced epigenetic variation.

methylation of this IAP element. These last observations increase the range of maternal ingestible compounds that might affect methylation in offspring but also broaden the range of mechanisms through which

Neural tube defects

they might directly or indirectly induce epigenetic

In view of the success of maternal folate supplementa-change.

tion in reducing the incidence of neural tube defects, it has been speculated that epigenetic mechanisms

Are diet-induced epigenetic changes

may be involved in the disease etiology and its prevention [28]. This hypothesis

is especially attractive restricted to a subset of genes?

given the epigenetic variability reported for the human The Avy model is unusual in that the mutation is caused AXIN1 gene. There are several mouse models of neural by the insertion of a retrotransposon upstream of the tube defects, many of which are folate responsive, but gene promoter. Invading retrotransposons appear to

despite the obvious efficacy of folate therapy, the mech-be a specific target for the methylation machinery, and anism of its action remains unknown [29]. As noted thus the effects of diet might be observed in simi-earlier, the effect of folate supplementation might larly affected genes. Indeed, the Axin1Fu mouse pro—

not be limited to the availability of methyl donors

vides another example of an IAP insertion in which

because this vitamin has pleiotropic effects including methylation can be manipulated by diet. The kinky—

effects on purine and pyrimidine synthesis, amino acid tailed phenotype of the Axin1Fu mouse results from

metabolism, and DNA, protein, and lipid methylation

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insertion of an IAP into the Axin1 gene, and the pen-

(Figure 18.3).

Section 3: Specialized requirements Human IVF demonstrates an

Mouse embryos show frequent epigenetic aber—

environmental effect

rations when exposed to an abnormal environment

and media. One of the earliest examples of this is

Data from human in vitro fertilization (IVF) suggest altered methylation and expression of specific genes that epigenetic perturbation is possible during the first in adult mice following nuclear transplantation [32].

few days of development. A petri dish of synthetic

More recently, aberrant loss of imprinting (biallelic media provides a markedly abnormal environment for

expression) of one or more genes occurred in 80% to

the developing embryo and there is evidence that this 90% of placentas and 17% of fetuses following embryo abnormal environment is associated with epigenetic

transfer and culture [33]. IVF shows an increased rate aberrations in children conceived by IVF. For exam-of epigenetic aberrations compared with culture alone ple, the incidence of Beckwith-Wiedemann syndrome

[34]. Mouse embryo culture has been associated with (BWS) appears to be increased, as is that of Angel-higher blood pressure in adult mice and changes in man syndrome (AS) [30]. In a population-wide study the activity of physiological regulators, suggesting that in Australia, the incidence of BWS was approximately culture-induced epigenetic changes can have a pheno—

9 times greater in children conceived by IVF than in typic impact [35]. In contrast, the phenotypic conse-the general population (i.e. 1 in ~4000 after IVF, com-quences of abnormal imprinting in mouse or human pared with 1 in ~36 000 in the general population).

placentas are not yet clear.

That children conceived by IVF who have BWS almost

A feature that clearly distinguishes some published

all share a single epigenetic defect – hypomethylation animal culture results from human IVF is the use of

of the KCNQ1OT1 gene promoter – provides addi—

serum within the culture media. The addition of serum tional evidence that the procedure itself is responsi-reduces viability of mouse embryos and was associated ble for the aberrant epigenetic modification. Although with a decrease in expression from both H19 and Igf2

epidemiological evidence for an increase in the inci-

(a pair of reciprocally imprinted genes) and a small dence of AS is less strong, the molecular studies of increase in H19 methylation [36].

many IVF-associated AS cases reveal a rare mecha—

Additional manipulation of the mouse culture

nism for AS (hypomethylation at the imprint control

environment may provide candidate procedures for

region), suggesting a causal association.

improvement of human and animal artificial repro—

If the abnormal in vitro environment of IVF can

ductive techniques. If the nutrient balance of the cul-induce major epigenetic aberration at low frequency, ture media alters epigenetic programming in embryos, then does IVF induce minor epigenetic change at

then not only is early nutrition important for chil—

higher frequencies? The observation that children con-dren conceived by IVF, it also suggests that the envi-ceived by IVF are, on average, taller with higher ronment provided by mothers in normal in vivo con—

insulin-like growth factor 1 (IGF-1) and IGF-2 lev—

ceptions may influence offspring. However, the rate of els and have more favorable lipid profiles than control imprinting abnormalities detected by molecular tech—

children, points to common changes with IVF [31].

niques (17%) in mice after embryo transfer and cul—

Furthermore, if perturbed environment within a petri ture is approximately 700-fold higher than the rate

dish can alter epigenetic programming, can an imbal—

of phenotypically detected imprinting abnormalities

anced in vivo environment do likewise? That is, can the in humans. Furthermore, the potential to modify the

periconceptual nutritional state of the mother affect nutrient composition of the human oviduct and uter—

the epigenome in naturally conceived children?

ine fluids may be insignificant compared to that occurring in vitro, and the lessons from IVF may not be easily generalizable to in vivo conception.

Epigenetic aberrations after animal

Mouse studies suggest that the composition of the

media is important in causing epigenetic aberrations, embryo culture

but other in vitro factors such as temperature fluctua-Animal studies certainly confirm the increase in epitions, absence of a hypoxia, or altered growth kinetics genetic abnormalities that can be associated with in may play a role. Furthermore, although animals clearly vitro embryo culture. However, the lessons from ani—

show epigenetic abnormalities from artificial repro—

mals might not be directly applicable to early human ductive techniques, it remains controversial whether **186**

embryo development.

humans do. Given that infertility itself appears to be **Chapter 18: Nutrition, environment, and epigenetics** associated with epigenetic abnormalities of the

sperm, include numerous epigenetic modifications that alter and an increase in BWS and AS, it is not clear how

the physiology of the developing organs.

many of the human IVF-associated imprinting abnor—

The ability to manipulate the maternal environ—

malities reflect the procedure versus infertility itself ment to optimize the health of offspring is a key focus [37].

of this chapter. This section considers the possibility that offsprings' epigenotypes can be altered by changes in maternal factors.

Cow and sheep IVF

The occurrence of aberrant phenotypes following in

Metabolic syndrome, diabetes, and insulin

vitro culture in cows and sheep has reinforced con—

resistance

cerns about the potential for human IVF to affect

phenotype. Large offspring syndrome, associated with There is considerable evidence that poor fetal growth cloning and embryo culture, is characterized by pla—

can influence the phenotype of adults. To explain the cental and fetal overgrowth with abnormal organ and

adult "memory" of fetal exposures, it has been spec—

skeletal development. In cultured sheep embryos, the ulated that these effects are mediated by epigenetic syndrome is associated with a reduction in methyla—

mechanisms, although the evidence so far remains

tion of the DMR that controls Igf2R imprinting, with scant.

consequent reduction in levels of IGF2R, explaining

A role for epigenetic modification has been pro—

the enhanced fetal growth [38]. It occurs after both posed, for example, in Type II diabetes on the basis cloning (nuclear transfer) and culture, but the mech-of observations that various maternal interventions in anisms are not necessarily the same, because cloning rats result in diabetes or insulin resistance in adult off- requires the additional step of erasure of somatic spring. Specific evidence for the involvement of epi-epigenetic modifications. Importantly, however, this genetic factors comes from observed changes in DNA

extreme example of embryo culture–associated epige—

methylation and histone modifications in offspring of netic aberration is predominantly associated with the rats with intrauterine growth restriction (IUGR). In use of serum in the culture media [39]. Not only does a commonly used model, a hypoxic, vascular insult this suggest a growth factor–related etiology, but the from bilateral uterine artery ligation 3 days before lessons are probably not applicable to human IVF, in birth rapidly induces IUGR, which is associated with which the use of serum is no longer recommended. At

reduced pancreatic beta-cell mass, reduced insulin

this stage, results from animal and human IVF do not secretion, insulin resistance, and, consequently, Type allow general conclusions to be drawn about the opti-II diabetes in adults. Within 24 hours of the onset of mal nutrient environment for the developing zygote.

growth retardation, the level of expression from the Pdx1 (pancreatic and duodenal homeobox 1) gene was

halved. Subsequently, histone modifications that are **Environmental effects during**

associated with gene silencing were observed in the

Pdx1 promoter, that is, histone deacetylation, reduced **embryogenesis**

histone 3 lysine 4 methylation, and increased histone 3

After early postimplantation development, the global lysine 9 methylation, along with increasing promoter DNA methylation status of an embryo and its extra—

DNA methylation as the animals age [42, 43].

embryonic tissues remains relatively stable. However, A change in epigenetic modification, however, does

continuing epigenetic modification does occur dur—

not necessarily reflect a causal effect. For example, ing the process of tissue differentiation. For exam—

DNA methylation can occur as a consequence, rather

ple, as neural progenitor cells differentiate from mouse than a cause, of gene silencing [44], whereas histone embryonic stem cells, numerous genes undergo epi-acetylation is a short-term labile modification that genetic modification, reflected by changes in his—

merely reflects the activity state of that gene rather than

tone modification [40], whereas differentiating embry-its long-term epigenetic state [45]. Many of the histone onic or extraembryonic cells, or differentiating fat modifications are more stable than acetylation, but the

cells show modifications of DNA methylation [11,

extent to which they contribute to long-term heritable

41]. In utero development, essentially an accumulat-gene activity states remains controversial [13, 14]. Epi-187

ing sequence of differentiation events, will obviously

genetic changes that have been reported to date might

Section 3: Specialized requirements

constitute part of the permanent metabolic memory

mechanisms have been considered as mediators of

that causes persistence of the diabetic phenotype into

these developmental changes.

adulthood, but they might also reflect physiological

Using the maternal low-protein (high-carbo—

changes mediated by other mechanisms. For example,

hydrate) rat model, methylation of, and expression

the memory of the fetal environment may reside pre—

from, the angiotensin II receptor, type 1b gene

dominantly within anatomical changes induced in the

(Agtr1b) has been studied [49]. The low-protein diet developing organs such as

the pancreas.

was associated with a reduction in Agtr1b methylation

Feeding pregnant rats with a low-protein (high—

from 22% in controls to 7% in the whole adrenal

carbohydrate) diet from conception to delivery pro—

of treated animals. Concurrently, threefold greater

vides another model that has been used to study epi—

expression of Agtr1b was detected in treated animals.

genetic modification. The glucocorticoid receptor and

Because Agtr1b expression is predominantly from the

PPAR␣ genes (GR and PPARA) have been the spe—

adrenal cortex, which constitutes only a small minor—

cific targets of study, because upregulation of their

ity of adrenal cells, the apparent correlation between

expression occurs with disturbed metabolic control

cortical expression and whole adrenal methylation

in rats. PPAR␣, one of the peroxisome proliferator—

requires further investigation.

activated nuclear receptors, has roles in fatty acid oxi—

Animal models, and some human epidemiologi—

dation, lipid metabolism, and inflammation, and its

cal data, point toward an association between mater—

expression is increased under conditions of fasting

nal diet and birth weight and the number of nephrons

to manage energy substrates for survival. Glucocor—

in adult kidney [50]. Retarded renal growth is possi-ticoid receptor, ubiquitously expressed in all tissues, bly associated with adult hypertension [51]. Although mediates the multiple roles of glucocorticoids, effec-epigenetic changes may be associated with the changes tors of the stress system. PPARA promoter methylation

in gene expression that accompany fetal kidney growth

has been quantified by using pyrosequencing of liver

retardation [52], it is also possible that altered anatom-DNA from offspring of pregnant rats fed a low-protein ical structures themselves could provide a legacy of the

(high-carbohydrate) diet [46]. The average methyla-uterine environment.

tion of PPARA was reduced from 6.1% to 4.5%, rais—

ing the possibility that profound dietary changes might

induce subtle, graded changes in the epigenotype. Previous studies have also suggested reduction in methy—

Postnatal programming

lation of the GR gene, but quantitative data are not yet

The potential for maternal effects on epigenetic modi—

available.

fication might not be restricted to pregnancy. Behav—

Nutritional studies in India point to associations

ioral changes in nursing rat mothers, which induce

between vitamin B12 and folate status, intrauterine

long-term physiological changes in offspring, might

growth retardation, and childhood insulin resistance.

affect DNA methylation. Mothers that exhibit high

In particular, high red cell folate levels were positively

levels of licking and grooming of their pups caused

associated with insulin resistance [47]. These find-increased expression of the estrogen receptor alpha in ings are interesting, particularly in view of the evi—

the hypothalamus, and of the glucocorticoid recep—

dence implicating altered B12 and folate with epige—

tor in the hippocampus in offspring. These changes

netic change in mice and sheep.

in receptor expression were paralleled by changes in

methylation of the 1b and exon 17 promoters, respectively; pups from high licking and grooming mothers

showing lower methylation for these genes than pups

Hypertension

from low licking and grooming mothers [53, 54].

Human epidemiological studies and animal models

It remains plausible, yet currently unproven,

both implicate a role for fetal undernutrition in adult

that epigenetic change can be induced after birth,

hypertension [48]. The in utero effects of altered mater-by changes in nutrition. Indeed, excessive catch-up nal diet include reduction in nephron number, mod—

growth in low birth weight infants is associated with

ification of the renin-angiotensin system, endothelial

long-term obesity [55], which might be mediated by dysfunction, and increased birth weight, confounded anatomical or physiological changes supported by epi-

by postnatal catch-up growth and obesity. Epigenetic

genetic modification.

Suggestions that DNA methylation within the

mum quantity of resources at the expense of offspring

brain shows plasticity and that nutritional status may

from other fathers. Conversely, the fitness of the mater—

be important in its maintenance herald the possibility

nal genome is enhanced if maternal resources are con—

that lifelong nutritional status may play a role in epige—

served and distributed to as many offspring as possible

netic programming [56]. However, evidence for this is during the mother's reproductive life.

provided only by a small group of preliminary reports

In accordance with the predictions of the conflict

of altered epigenetic DNA methylation.

hypothesis, the effect of parental imprinting on placental growth and efficiency differs between mater-

Altered epigenetics during germ cell

nally and paternally expressed genes. That is, in

general, paternally expressed (maternally suppressed)

development

imprinted genes enhance placental growth, surface

Modification of the germ cells constitutes completion

area, and nutrient transport, whereas the maternally

of the epigenetic cycle, albeit in a specialized branch

expressed genes suppress placental growth [60].

of development distinct from the other somatic tis—

By using knockout mouse models to reduce the

sues of the embryo. Epigenetic marks required for suc—

number of functional copies of the imprinted genes

cessful imprinting and differentiation of the embryo

even further (i.e. to zero), the role of imprinting in

are erased in the early germ cells in preparation for

placental growth can be inferred. These mouse mod—
totipotency. During this erasure or reprogramming,
els suggest that a role of maternal suppression of Igf2,
there is substantial loss of repressive epigenetic modi—
Peg1, and Peg3 is to decrease placental size. Simi—
fications such as DNA methylation and repressive his—
larly, knockout of paternally suppressed genes, Igf2r,
tone methylation (e.g. histone 3-lysine 9 dimethyla—
Cdkn1c, H19, Phlda2, and Grb10, results in enhanced
tion) [57].
placental growth. Therefore, by controlling the size of
Subsequently, during germ cell maturation and
the placenta during normal development, epigenetic
gametogenesis, a new round of epigenetic modifica—
control of these imprinted genes has the potential to
tions is applied to this “clean slate.” Presumably within
control global nutrient transfer to the fetus.
germ cells, oocytes, and sperm, epigenetic modifica—
More detailed assessment has confirmed key func—
tions are applied to restrict gene expression to a rele—
tional roles for some of these genes. Igf2, for exam—

vant subset of developmental genes. In addition, dur—

ple, has a placenta-specific transcript (P0), deletion of

ing gametogenesis, it is critically important to mini—

which results in marked placental growth retardation

mize activity and mobility of retrotransposons within

[58]. The constraint on fetal growth imposed by the the genome. These repetitive retroelements are held in small placenta is demonstrated by postnatal catch-up

check by DNA methylation [3], preventing increased growth. Although the efficiency of the small placenta mutational load in the species.

was shown to be enhanced, it was clearly insufficient

to meet the nutritional requirements of the develop—

Impact of imprinted genes on resources and

ing fetus. The placentomegaly that results from loss of

Igf2 imprinting (which causes a double dose of Igf2)

placental growth

confirms the role of maternal suppression of this gene

The focus of the previous sections has been on poten—

in restricting resource allocation to her offspring. In

tial effects of maternal nutrients on epigenetic mod—

addition, these models demonstrate the requirement

ifications. In addition, the epigenetically controlled

for coordinated supply (placental) and demand (fetal)

imprinted genes appear to play a major role in con—

and point to the possibility that uncoordinated growth

trolling nutrient transfer at the maternal-fetal interface

may have maladaptive consequences such as excess

[58, 59]. Because genomic imprinting arose at the time postnatal catch-up growth, with its negative conse-of evolution of lactation and placentation, we have pro-quences in adult life [55].

posed that imprinting has a key role in the alloca—

The coordination between placental nutrient sup—

tion of maternal resources across the placenta to the

ply and fetal demand is further demonstrated by

developing embryo. The conflict, or kinship, theory

the crosstalk between paternally expressed Igf2 and

of imprinting evolution postulates a conflict between

another imprinted gene Slc38a4. When Igf2-controlled

maternal and paternal genomes, in that the fitness of

fetal demand exceeded supply, Slc38a4, a System

the paternal genes is enhanced by extracting the maxi—

A amino acid transporter, was upregulated, thereby

Section 3: Specialized requirements

increasing placental efficiency [61]. The interaction situations, good food supply

was associated with an between paternally expressed Igf2 and paternally increased risk of premature death in the grandchildren expressed Slc38a4 shows the importance of epigenetic [64].

gene regulation (i.e. genomic imprinting) in control—
The ability to inherit the consequences of grand—
ling nutrient demand and supply. In addition, the roles
parental food supply suggests the occurrence of trans—
of both proteins are consistent with the hypothesis that
generational nongenetic inheritance. Although the
paternally expressed imprinted genes contribute to the
mechanism has yet to be determined, these obser—
extraction of maternal resources. Reciprocally, sup—
vations raise the possibility that germline epige—
pression of the maternally inherited allele is an impor—
netic marks can survive germ cell reprogramming
tant mechanism by which a mother controls the allo—
and zygotic demethylation. Importantly, transmission
cation of her resources, thus enhancing her lifelong
through the paternal line appears to exclude maternal
reproductive fitness.

lineage effects (discussed later). Confirmation of these

A key question is whether physiological or patho—

results and determination of the mechanism of trans—

logical alterations within the cells that give rise to

mission might have implications for future nutritional

the trophoblast and placenta during the first 3 to 4

manipulation.

days of life can additionally influence placental func—

When considering maternal transgenerational

tion. In mice, as noted earlier, embryo culture and IVF

transmission, it is important to consider that a change

are associated with a high rate of aberrant methyla—

in the maternal environment could potentially exert

tion of imprinted genes in the placenta. In cattle, pla—

direct epigenetic and genetic effects on the offspring

centomegaly is a prominent feature of the large off—

itself but also, through modification of the offspring's

spring syndrome, which is associated with embryo

germ cells, the subsequent generation (i.e. grand—

culture [38]. It is interesting to note that in vitro– children). The following generation is, therefore, the

produced pregnancies were associated with increased

first to be not directly exposed to the environmental

glucose and fructose accumulation in fetal plasma and

exposure of interest, and thus, it is not until this third

associated fluids, suggesting that placentomegaly and

generation that one can conclude the occurrence

enhanced transport capacity are closely related [62]. In of transgenerational inheritance of an epigenetic addition, in humans, placental overgrowth is a charac—

modification [65].

teristic feature of the somatic overgrowth imprinting

For intergenerational epigenetic inheritance to

disorder Beckwith-Wiedemann syndrome [63].

occur, a modification within a gamete must survive

A more subtle response to an altered nutritional

the epigenetic programming that occurs in the zygote.

environment at conception might lead to modula—

As imprinted genes attest, not all DNA methylation

tion of placental imprinting. This would result in a

is erased in the zygote, given that approximately

direct relationship between maternal nutritional state

20 imprint control regions must maintain differen—

and feto-placental growth at the earliest stages of

tial methylation throughout this stage. In addition

development.

to imprint gene control regions, it is known that

the methylation of IAP retroelements is relatively

Transgenerational epigenetic

resistant to erasure in the zygote [66]. The extent to which these and other gametic modifications survive **modification**

the postconception erasure essentially defines the

The earlier sections have considered the potential for

potential for intergenerational epigenetic inheritance.

a mother to modify her offspring epigenetically, but to

Germline epigenetic marks that survive zygotic

what extent can the effects of the maternal or pater—

reprograming to manifest themselves in the second

nal environment induce any transgenerational epige—

generation are indeed of considerable interest, in

netic effects? Epidemiological evidence highlights the

that it would provide a mechanism by which the

potential for grandparental nutrition to impact on

environment of the grandmother could affect the

the phenotype of the grandchildren. The food sup—

grandchild’s phenotype. Epigenetic inheritance for an

ply of paternal grandfathers during their prepubertal

additional generation (i.e. true transgenerational

slow growth period (age 9–12 years) has been linked

inheritance) has the additional requirement of surviv—

to the mortality of the grandsons, and that of the

ing the reprogramming that occurs in primordial germ

paternal grandmothers to the granddaughters. In both

cells.

Table 18.1 Examples of putative epigenetic modifications associated with environmental factors or ancestral phenotypes **Putative epigenetic Timing**

Factor

Model

modification

References

Grandparental

Food supply

Human

Unknown

Transgenerational

Endocrine disruptors

Rat

DNA meth

Maternal soma and

Maternal coat color

Avy mouse

DNA meth

germ cells

Parental soma and

Parental tail shape

Axin1Fu mouse

DNA meth

germ cells

Paternal germ cells

Nuclear transfer

Mouse

DNA meth

Periconception

Methyl donor “deficiency”

Sheep

DNA hypometh

Periconception

Methyl donor supplements

Avy and Axin1Fu mice

DNA hypermeth

[21], [26]

Periconception

In vitro fertilization

Human

DNA hypometh at

KCNQTOT1, SNRPN

Periconception

Embryo culture, in vitro

Mouse

Altered DNA meth

[33], [34]

fertilization

Periconception

Embryo culture (with serum)

Cow, sheep

DNA hypometh at IGF-2R

Embryogenesis

Placental ischemia with

Rat

Altered histones; DNA meth

[42], [43]

intrauterine growth restriction

at Pdx1

Embryogenesis

Maternal

Rat

Reduced DNA meth at

low-protein/high-carbohydrate

Ppara

diet

Embryogenesis

Maternal low-protein/high—

Rat

Reduced DNA meth Agtr1b

carbohydrate diet

Postnatal

Maternal behavior

Rat

Altered DNA meth gene

[53], [54]

name ERA, GR?

It is further important to distinguish maternal epi—

urinary protein (MUP), as well as reduced adult body

genetic inheritance from maternal lineage effects: a

weight [32]. Importantly, probable transgeneration phenotype could be inherited through the maternal epigenetic inheritance occurred after transmission to

lineage simply because of altered phenotype of the

the next generation through the male germline [68].

mother, causing altered phenotype of the daughter and

More than half of the offspring of manipulated males

so on. There is, for example, a consistent positive corre—

showed similar reduction of MUP expression, along

lation between the birth weights of mothers and their

with increased Mup methylation. Furthermore, adult

offspring, the consequence of which is to perpetuate,

body weight was also reduced in these offspring.

over multiple generations, the phenotypic response to

As noted earlier, the phenotype of Avy mice

food deprivation [67]. Fortunately, maternal lineage depends on the degree of methylation of an IAP retro-effects can be experimentally dissociated from mater-transposon within the agouti gene promoter. Com—

nal epigenetic inheritance by embryo transfers.

pared with those with agouti (yellow) coat color,

agouti mothers with a normal coat color (i.e. heav—

ily methylated IAP) have a higher proportion of off—

Lessons from animal models

spring with normal coat color, suggesting the persis—

Manipulation of early embryos, by culture or nuclear

tence of an epigenetic signal through erasure in the

transfer, is associated with perturbed epigenetic mod—

germ cells and post fertilization [22]. Thus, the moth-ifications, some of which may be capable of transgeners' gametes carry an epigenetic record that parallels erational transmission. For example, manipulation of

her somatic phenotype, and this record is not com—

zygotes by transfer of the pronuclei into recipient eggs

pletely erased in the zygote. Similar observations with

of a different genetic background resulted in increased

respect to parental transmission of the kinky-tail phe-

gene methylation and repressed expression of major

notype of the Axin1Fu mouse support the case that

Section 3: Specialized requirements

transgenerational epigenetic inheritance can occur

of these drugs were transferred through the male

[25]. Curiously, the Avy IAP is completely demethy-germline to the fourth generation of offspring, with lated in the early embryo, showing that the intergenera penetrance inconsistent with genetic inheritance.

ational epigenetic mark may not be DNA methylation

Epigenetic differences were observed in affected F2

[69].

to F4 mice, suggesting that the phenotype may be

The next question is whether nutritional manipula—

attributable to nongenetic mechanisms. Thus, the

tion of an F0 mother can alter the long-term epigeno—

potential for transgenerational inheritance has been

type of the “unexposed” grand (F2)-offspring. Indeed

demonstrated, suggesting that the epigenetic repro—

Cropley *et al.* showed that a high-methyl-donor sup—

graming that occurs during germ cell development and

plemented maternal (F0) diet (vitamin B12, folate,

after fertilization can potentially be circumvented by

betaine, choline, zinc, and methionine) normalized

undefined mechanisms.

not only the coat color of the F1 offspring (maternal

effect) but also that of the F2 generation [70]. Because the germ cells of the F1 females were exposed to, and **Summary**

presumably modified by, the supplemented diet dur—

Epigenetic modification provides an important mech—

ing their embryogenesis, this experiment indicates that

anism through which the totipotent resources of the

the oocyte-associated epigenetic modifications are not

genome are managed to create tissue-specific differ—

completely erased in the F2 zygote. Thus, this dietary

ences in gene expression and cellular function. In

intervention experiment is consistent with previous

addition to its role in specifying tissue differentia—

observations that a mother’s somatic epigenotype can

tion within an individual, studies in genetically iden—

influence the epigenotype of her offspring.

tical animals indicate the potential for epigenetic

Can these modifications be transmitted yet another

modification to create interindividual phenotypic

generation and influence the epigenotype of F3 off—

variation. A wide range of environmental changes

spring, the true test of transgenerational inheri-

(Table 18.1), including in vitro embryo culture, dietary tance? [65] When Avy mice were fed with methyl-methyl donor content or protein-carbohydrate bal- supplemented diets for successive generations, there ance, tissue ischemia, and possibly maternal behavior,

was no cumulative effect across generations, suggest—

have the capacity to modify an organism's epigenome.

ing that diet-induced epigenetic change is not inher—

The extent to which such factors contribute to adult

ited in a transgenerational manner [19].

phenotypes and common diseases is an area of

Although a role for diet in mediating transgener—

intense research activity. Furthermore, the extent

ational epigenetic inheritance has not been demon—

to which acquired epigenetic modifications can be

strated, such inheritance has been observed after

transmitted to future generations is of great inter—

exposure of rats to estrogenic and antiandrogenic

est for biomedicine. It is likely that future recom—

endocrine disruptors (methoxychlor and vinclozolin,

mendations for maternal nutrition and postpartum

respectively) that induce decreased spermatogenic

behavior will be, in part, based on their epigenetic

capacity and increased infertility [71]. The effects consequences.

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