Advances in fertility control and the treatment of sterility

Advances in FERTILITY CONTROL and the TREATMENT OF STERILITY

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1
Pre-treatment evaluation of ovarian infertility

G. BETTENDORF

ABSTRACT

Pretreatment evaluation of a disease means to evaluate a diagnosis in the individual patient according to which a proper selection of the type of treatment is indicated.

In respect to ovarian dysfunction as a cause for infertility, the endocrine status has to be evaluated. Patients can be divided into oestrogen positive and oestrogen negative. In the last mentioned group further sub-grouping has to be done according to the FSH and LH concentration. For both oestrogen positive and oestrogen negative patients the prolactin and the androgen status as well as the thyroid function has to be tested.

Having the information on the oestrogen, the gonadotrophin, the prolactin, the androgen and the thyroid status of the individual patient the basis for the selection of the type of stimulation therapy can be given.

Infertility is a diagnosis applied to a couple. Clinical examination with endocrinological tests in both partners will enable the physician to evaluate defects in the reproductive functions: ovarian dysfunction associated with amenorrhoea, oligomenorrhoea, polymenorrhoea or anovulatory cycles and luteal insufficiency.

There is a continuous transition between normal ovulatory cycles, luteal insufficiency and anovulatory cycles to amenorrhoea. There is insufficient follicular maturation followed by ovulation and defective luteal function or no ovulation and luteinization. The *corpus luteum insufficiency* is a distinct and common form of infertility. Irregular patterns of the menstrual cycle are common.

Anovulatory cycles mostly are combined with irregular cycles, there is follicle growth and steroid production but no ovulation and no luteal function. In many women a gamut of different functional patterns may be observed in consecutive cycles. Cycles with obvious luteal insufficiency may be interspersed between perfectly normal ovulatory ones which, in turn, may be replaced by anovulatory cycles.

In amenorrhoea there is no follicle growth and no oestrogen production which leads to endometrium proliferation and bleeding. The causes of these different symptoms of ovarian dysfunction are as follows:

(1) Insufficient stimulation.
(2) Primary ovarian dysfunction.
(3) Elevated androgens (ovary or adrenal).
(4) Elevated prolactin.
(5) Thyroid dysfunction
(6) Diabetes.
(7) Nutritional (starvation or obesity).
(8) Drug induced.
(9) Psychogenic.

For the examination of the functional state the activity of ovarian hormones (oestrogen) and of those hormones that influence ovarian activity (gonadotrophins, prolactin, androgens, corticoid and thyroid hormones) have to be tested, either by clinical methods or by assays.

The oestrogen activity is a measure of ovarian activity which is dependent on hypothalamo-pituitary stimulation. By simple clinical methods the oestrogen situation can be tested. In patients with spontaneous bleedings there must be an oestrogen activity; the same applies in those who respond with a bleeding following progestin medication. The cervical gland is a very sensitive target and reacts

with mucus production under the influence of oestrogens; the vaginal epithelium shows maturation. All these parameters can be checked very easily and give good information on the oestrogen activity. Only in special situations (e.g. during HMG therapy) do analytical procedures have to be taken for exact measurement of oestrogen concentration, either by chemical procedures or by immunoassays:

(1) Clinical tests:
   (a) Endometrium – (i) spontaneous bleeding; (ii) progesterone-induced bleeding (progestin test).
   (b) Cervix – (i) spontaneous secretion; (ii) oestrogen-induced secretion.
   (c) Vaginal cytology.
(2) Analytical tests: serum oestradiol levels and total urinary oestrogens.

Androgens are produced in the ovary and in the adrenal gland. Hyperandrogenism clinically is diagnosed by symptoms such as acne, hirsutism and virilization. The blood concentration of testosterone, androstenedione and dehydroepiandrosterone can be measured. A normal adrenal and thyroid function is essential for a physiological ovarian activity; in functional disturbances therefore the adrenal and thyroid hormones have to be tested:

(1) Clinical tests – virilization, acne and hirsutism.
(2) Analytical tests – testosterone and androstenedione levels.

The status of the pituitary cannot be tested clinically. But there is a strong correlation to the oestrogen activity: when there are oestrogens there must be a stimulation of the ovaries by the pituitary and direct measurement of FSH and LH will not give further information. In those cases where no oestrogen activity is found, pituitary function can only be evaluated by measurement of FSH and LH, which will result either in elevated or in subnormal values. In addition the pituitary reactivity can be tested by the LH-RH test, but this will not give additional information for further clinical procedures. A circhoral fluctuation of the LH concentration is found in normal ovarian function. In hypothalamic amenorrhoea this fluctuation is seized. In cyclic ovarian insufficiency changes in the LH fluctuation, either in frequency or in amplitude, can be found:

(1) Clinical test – correlation to oestrogen activity.
(2) Analytical tests – FSH, LH, LH-RH and LH fluctuation.

It is well known that *prolactin* is involved in ovarian function. Elevated prolactin leads to ovarian insufficiency. Clinically galactorrhoea is mostly combined with hyperprolactinaemia. But for proper evaluation prolactin has to be measured. Several stimulation tests are of questionable value:

(1) Clinical tests – galactorrhoea.
(2) Analytical tests — prolactin, TRH, metoclopramide and sulpiride stimulation.

Various proposals for pre-treatment evaluation of ovarian dysfunction and for their classification have been made. The first WHO classification (1973) was based on the endogenous oestrogen activity and the level of gonadotrophins. Group I comprised patients with amenorrhoea and with little or no evidence of endogenous oestrogen activity. Group II comprised women with a variety of menstrual cycle disturbances including amenorrhoea, who exhibited distinct endogenous activity and gonadotrophins in the normal range. Group III comprised women with primary ovarian failure associated with low endogenous oestrogen activity and elevated gonadotrophins. This classification was revised in 1976 and the prolactin status was added to the above-mentioned groups. The androgen, corticoid and thyroid hormones were not considered.

A pre-treatment classification in particular should meet therapeutic aspects. The diagnosis, as correct as possible, should be found within a short period of time with a minimum of expenses.

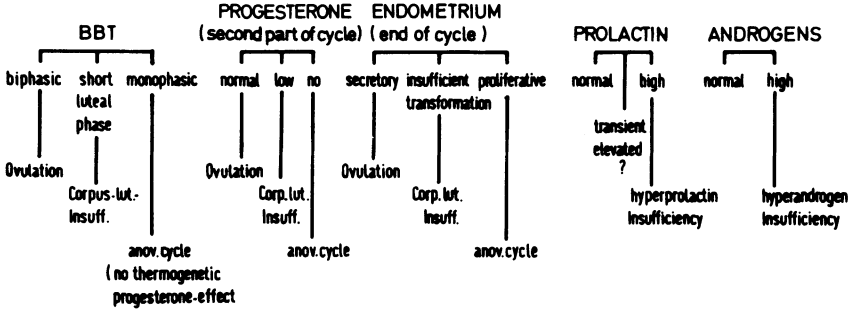

Figure 1 Diagnostic evaluation of ovarian dysfunction in patients with spontaneous bleedings

Diagnostic tools for evaluation of ovarian dysfunction are:

(1) Clinical tests – history, general examination, gynaecological examination, cervical factor, vaginal smear, endometrium biopsy, progestin level and ovarian biopsy.
(2) Analytical tests – oestrogens, progesterone, androgens, gonadotrophic (basic level, ratio, fluctuations), prolactin and thyroid hormones.

In patients with menstrual-cycle disturbances ovarian function can be mainly checked by clinical methods. The pattern of the basal body temperature indicates a biphasic or ovulatory cycle, a short hyperthermic phase means luteal insufficiency and a monophasic pattern suggests an anovulatory cycle. The results can be supported by testing of progesterone levels either by direct measurement in the second part of the cycle and/or by the histology of the endometrium at the beginning of bleeding. For further evaluation prolactin and androgen estimations are necessary (Figure 1).

In amenorrhoea clinical tests enable the physician to differentiate between those patients with endogenous oestrogen activity and those who have none. This can be done by examination of the cervical factor, by the progestin test, by the endometrium biopsy or by the vaginal cytology. By additional analytical procedures FSH/LH measurement can characterize patients in those with high, normal or low gonadotrophins. The frequent measurement of LH shows if the LH fluctuation is normal, irregular in frequency or amplitude or if there is no fluctuation. Of further importance is the LH:FSH ratio and, as in spontaneous bleeders, the prolactin and androgen situation (Figure 2).

The diagnostic work-up results in a treatment-orientated classification of ovarian insufficiency. It should be emphasized that this in particular is possible by a careful clinical and gynaecological examination, which is supplemented by a few laboratory parameters.

The ovulation-induction era started 23 years ago. At first gonadotrophins became available followed by clomiphene, LH-RH and prolactin inhibitors. Direct stimulation of ovarian function is possible by FSH-LH preparations. Pituitary stimulation is possible by pulsatile LH-RH administration. Clomiphene acts via hypothalamo-pituitary stimulation and leads to normalization of ovarian function. Prolactin inhibitor normalizes the prolactin levels; corticoids can normalize the androgen levels in this way leading to improvement of ovarian

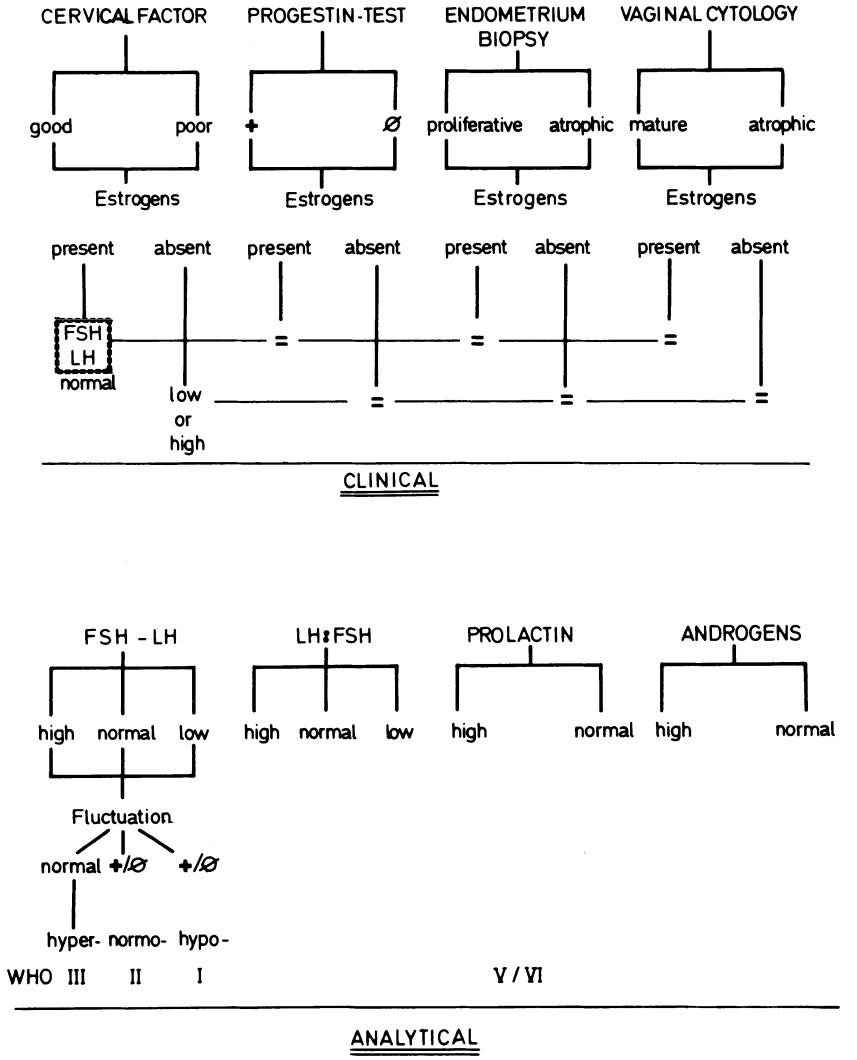

Figure 2 Diagnostic evaluation of ovarian dysfunction in patients with amenorrhoea (+/Ø = LH fluctuation irregular in frequency or in amplitude, or no fluctuation)

function. In addition it should be mentioned that the nutritional factors, psychic conditions and the whole environment are involved in normal ovarian or better reproductive function. The factors entailed can be summarized as follows:

(1) Direct – FSH/LH (hMG/hCG)
(2) Via pituitary stimulation (LH-RH)
(3) Via hypothalamo-pituitary stimulation (clomiphene)
(4) Via normalization of:
    (a) Prolactin status – prolactin inhibitor
    (b) Androgen status – corticoids
    (c) Thyroid function – thyroid hormones
(5) Via normalization of nutritional factors, psychic condition (psychotherapy) or environment (psychosocial)

After performing the pre-treatment examination of the patients, the physician comes to a diagnosis, which enables him to select the type of treatment and to be of prognostic value (Figures 3 and 4).

Pulsatile LH-RH is effective in patients with no oestrogen activity,

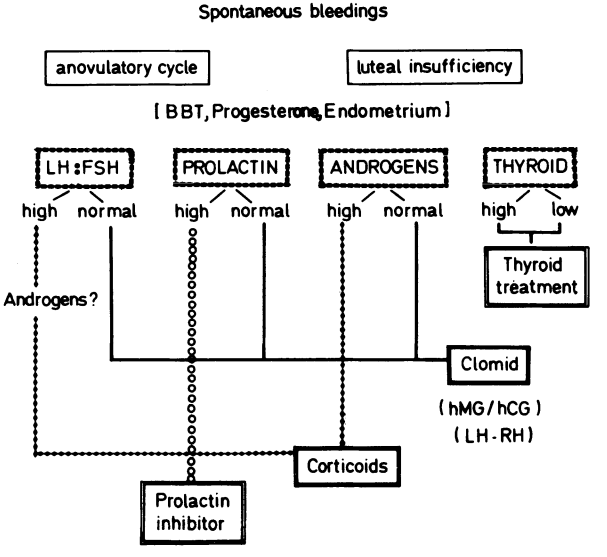

Figure 3 Treatment-oriented classification of ovarian dysfunction in patients with spontaneous bleeding

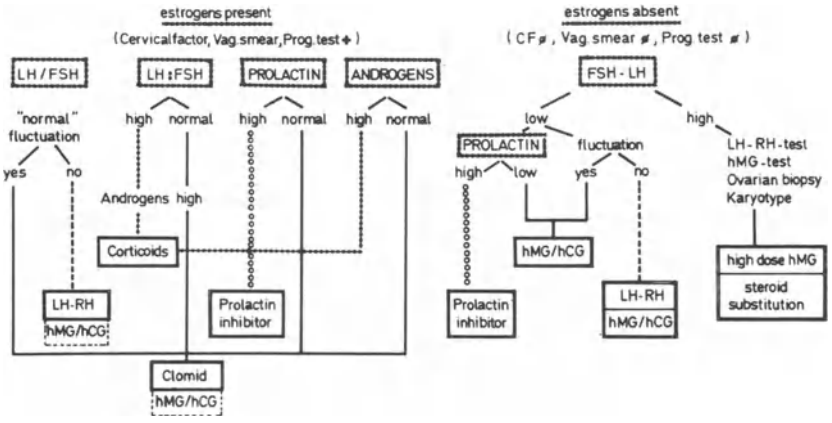

Figure 4 Treatment-oriented classification of ovarian dysfunction in patients with amenorrhoea

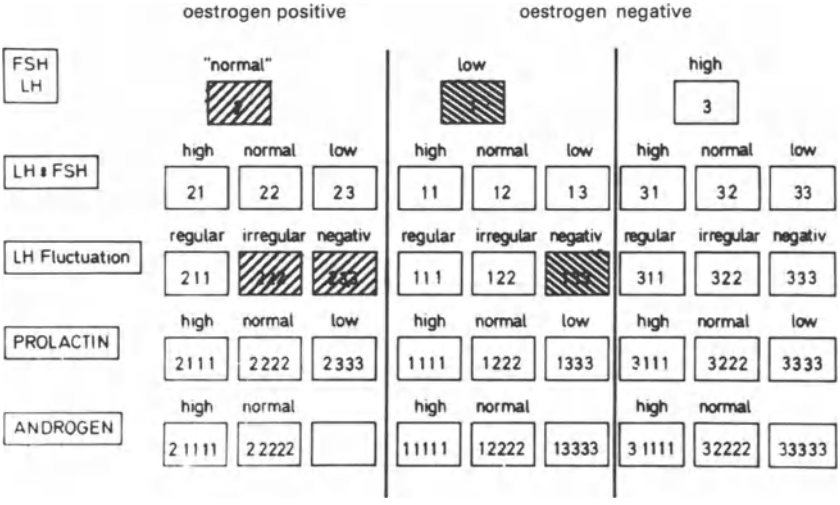

Figure 5 Indications for treatment with LH-RH (hatched area those in which the indication for this type of treatment is given)

low and stable LH levels and no or irregular LH fluctuation (Figure 5). hMG/hCG is effective in patients with no oestrogen activity, low FSH/LH levels and clomiphene failure (Figure 6). Clomiphene is effective in patients with oestrogen activity, or with low-to-normal FSH/LH values in luteal insufficiency, anovulatory cycles or amenorrhoea (Figure 7). Prolactin inhibitors are effective in patients with hyperprolactinaemia (Figure 8) and corticoids with elevated androgens (Figure 9).

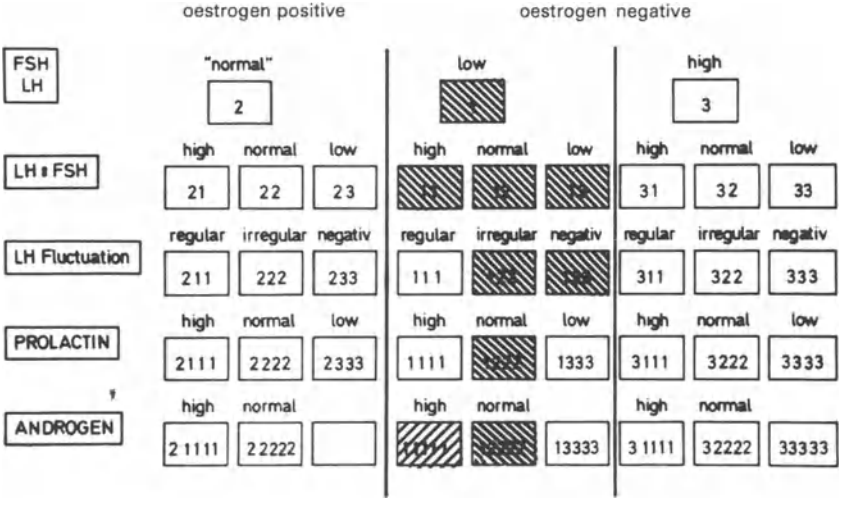

Figure 6 Indications for treatment with hMG/hCG

The most effective and most intensively studied treatment is that with hMG/hCG. With this ovarian stimulation in nearly all patients with ovarian dysfunction, stimulation with ovulation is possible. In the other types of treatment there is always a group of patients in whom ovarian function cannot be normalized; mostly the reason cannot be found. Sometimes combination therapy is effective in those patients; for example, clomiphene plus hCG, prolactin inhibitor plus clomiphene, and corticoids with clomiphene.

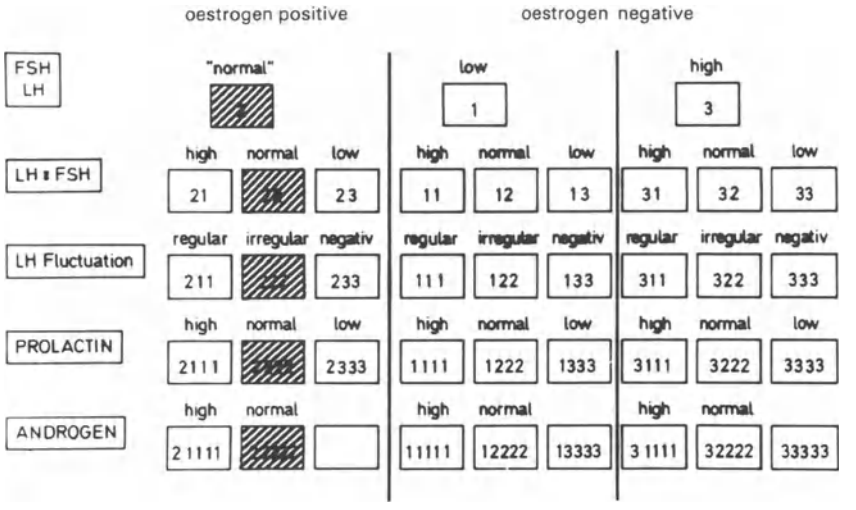

Figure 7 Indication for treatment with clomiphene

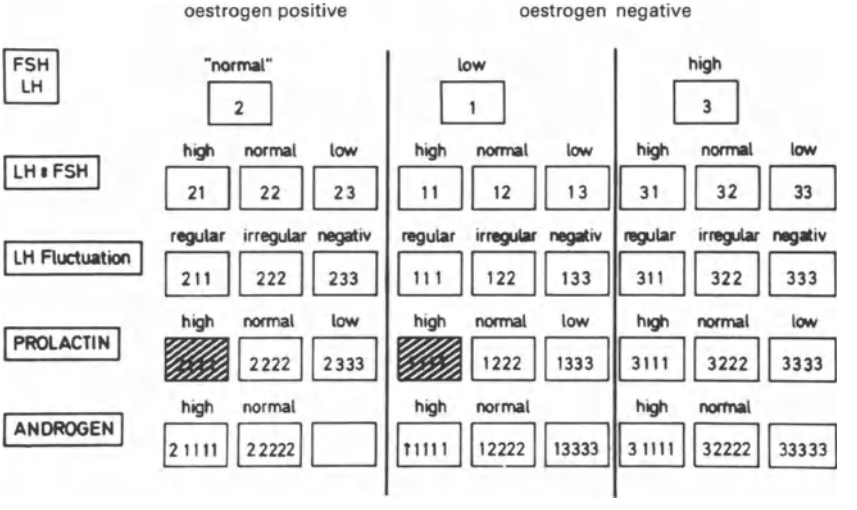

Figure 8 Indication for treatment with prolactin inhibitors

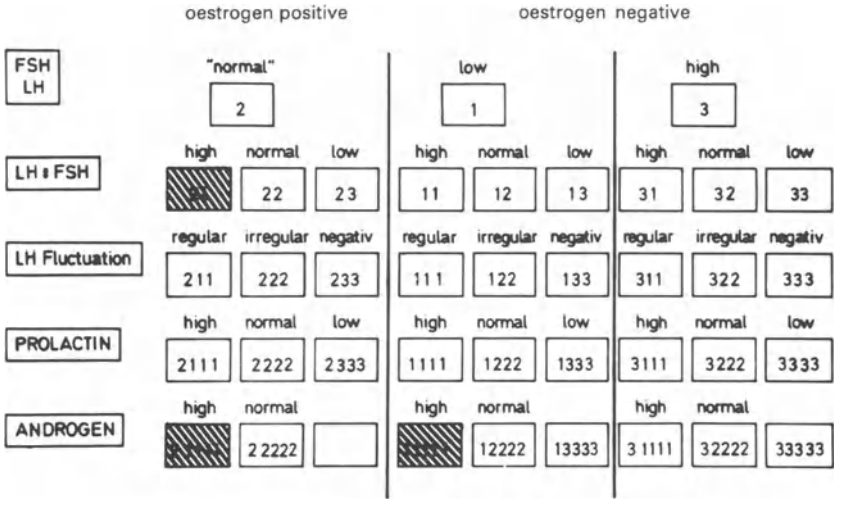

Figure 9 Indications for treatment with corticoids

Mostly pregnancy occurs during the first three treatment cycles in all therapeutic trials and it is obvious that the results after five or six treatment cycles are markedly reduced. Dealing with the infertile couple, one always should remember that there may be additional factors and that after some time treatment should be stopped and the diagnosis re-evaluated.

2
Hyperprolactinaemic infertility: some considerations on medical management

M. O. THORNER, M. L. VANCE and R. M. MACLEOD

ABSTRACT

Hyperprolactinaemia is a common cause of infertility in women. The most common cause for hyperprolactinaemia (after excluding ingestion of medications which elevate prolactin) is a pituitary tumour. These tumours can either be small (diameter less than 10 mm) = microadenomas, or, if greater than 10 mm, are termed macroprolactinomas. Although this distinction is arbitrary, it is often useful in predicting the outcome of transsphenoidal surgery, although the basal serum prolactin is a better predictor.

Irrespective of the size of the tumour or the pretreatment prolactin level, medical treatment with dopamine agonist drugs (e.g. bromocriptine, lisuride and pergolide) is effective in >80% of cases in lowering prolactin levels and in restoring gonadal function. The large tumours undergo volume reduction under this form of therapy. The potential problem of tumour expansion during pregnancy which is a function of the pre-existing tumour is reviewed. This risk appears extremely small in microadenomas but may be clinically significant in 10–25% of macroadenoma patients. The dilemmas of the management of this controversial problem are discussed.

INTRODUCTION

Since human prolactin was isolated and characterized 13 years ago, the study of the control of prolactin secretion has been intensive. Hyperprolactinaemia is the most commonly identifiable hypothalamic pituitary disorder[1,2]. The dominant inhibitory nature of hypothalamic control of prolactin secretion may be the reason that hyperprolactinaemia is such a common condition. During the past decade two separate therapeutic approaches to the management of hyperprolactinaemia have been introduced: transsphenoidal selective pituitary microsurgery and medical therapy to suppress prolactin secretion with orally active long-acting dopamine agonist drugs. Small prolactin-secreting tumours are treated extremely satisfactorily both with medical and with surgical therapy, both in terms of lowering serum prolactin levels to normal and in restoring gonadal function. However, for the larger tumours, either where the tumour is invasive or the pretreatment serum prolactin level is greater than 250 ng ml^{-1} the results of surgery are poor in terms of restoring to normal circulating prolactin levels and gonadal function[3–5]. We now discuss the medical management of hyperprolactinaemia, potential problems during pregnancy and the management of large prolactin-secreting pituitary tumours.

Although hyperprolactinaemia can occur in adolescence, during the middle years and in old age, it is usually recognized in patients between the ages of 20 and 35. The presentation of hyperprolactinaemia varies between women and men. Women usually present with menstrual abnormalities, amenorrhoea, oligomenorrhoea, and menorrhagia, or regular cycles with infertility. In addition, women often note a decrease in libido and dyspareunia due to oestrogen deficiency. There are often no characteristic findings on physical examination; however, the breast tissue is well preserved, Montgomery tubercles are prominent and galactorrhoea is sometimes present. Galactorrhoea is a poor discriminator for the presence or absence of hyperprolactinaemia, as it may occur in women with normal prolactin levels and may be absent in patients with extremely high serum prolactin levels[6]. The reason for this is that galactopoiesis is dependent on a complex interaction of many hormones, of which prolactin is only one, albeit an essential one. The incidence of galactorrhoea in women with hyperprolactinaemia varies from 30 to 82%[1,7] and in men it is present in 20–30%[8–10]. In men the usual presentation

is with symptoms due to expansion of the tumour giving rise to headache, and/or visual field defects due to compression of the optic chiasm. In addition men often suffer from impotence and loss of libido and have a hypogonadal appearance, being overweight and demonstrating reduced beard growth. The circulating testosterone levels are low, thus providing biochemical documentation of the hypogonadal state that is suspected clinically.

EVALUATION OF HYPERPROLACTINAEMIA

The major prolactin-inhibiting hormone is the catecholamine dopamine. Hyperprolactinaemia may, therefore, result from ingestion of drugs that either prevent the synthesis of dopamine or deplete its stores (e.g. α-methyl-dopa and reserpine, respectively) or block dopamine receptors on lactotrophs (e.g. phenothiazines, butyrophenones, or benzamides). Oestrogens act directly at the pituitary to stimulate lactotrophs and increase prolactin synthesis; this is associated with lactotroph hypertrophy. Occasionally primary hypothyroidism may be associated with mild hyperprolactinaemia and hence thyroid function tests should always be performed in these patients[11]. In young women hypothyroidism may present only with menstrual problems, without any of the usual symptoms or clinical stigmata. Drug-induced hyperprolactinaemia and that due to hypothyroidism usually results in relatively minor elevations of serum prolactin level, rarely to greater than 100 ng ml^{-1}. Pituitary tumour is the most common cause of hyperprolactinaemia. Such tumours are often subdivided into microadenomas or macroadenomas[3]. The microadenoma is defined as a tumour found at surgery with a diameter of less than 10 mm and associated serum prolactin levels are usually less than 200 ng ml^{-1}. It is now, with the advent of the high-resolution CT scanner, possible for these tumours to be diagnosed prior to surgery[12]. In the past there was considerable controversy about the radiological appearance of microadenomas, based on changes in the contour in the pituitary fossa seen on polytomography. It is now clear that many of the 'specific' changes were probably non-specific and represented normal variants. Although these problems have been circumvented with the later generations of CT scanners, a new problem has now arisen. Since microadenomas probably are found in a proportion of the 'normal' population the radiographic presence of a

microadenoma may not necessarily be synonymous with the lesion responsible for the hyperprolactinaemia.

We evaluate our patients with hyperprolactinaemia by taking a full history and performing a thorough physical examination. Particular emphasis is placed on looking for signs of hypothyroidism, evaluating the visual fields, and examining for signs of gonadal dysfunction. The most useful single investigation is the measurement of serum prolactin in the basal state on two or three independent visits. Repeated measurement is obviously not necessary if the first value is found to be extremely high (e.g. greater than 500 ng ml^{-1}). We also evaluate thyroid function by measuring a serum thyroxine, T_3 resin uptake, and a serum TSH. To determine whether there is any structural lesion in the pituitary we perform a high-resolution CT scan. We normally perform a visual field assessment using the Goldmann apparatus. Other endocrine testing of ACTH, GH, and gonadotrophin reserve is performed only if indicated.

DOPAMINE AGONIST THERAPY

The dopamine agonist ergot derivatives are effective when given by mouth. These drugs include bromocriptine, lergotrile, lisuride and pergolide. They act by binding to specific dopamine receptors on the lactotrophs. Each of these compounds appears to be long-acting and thus can suppress prolactin secretion throughout a 24-hour period. After a single 2.5 mg dose of bromocriptine prolactin levels are suppressed by approximately 80% in hyperprolactinaemic subjects

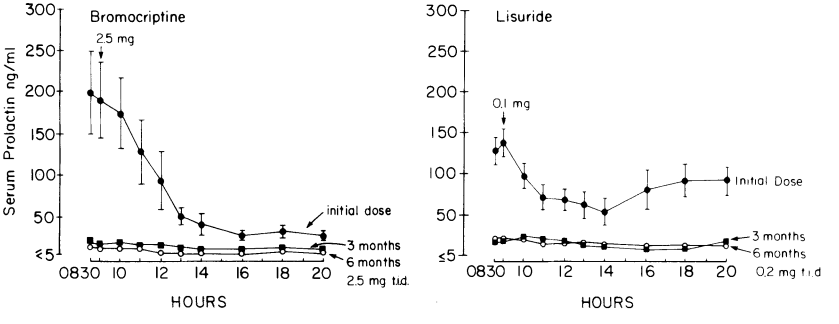

Figure 1 Serum prolactin levels in seven hyperprolactinaemic women after bromocriptine administration (left) and in six hyperprolactinaemic women after lisuride administration (right). The effects of a single acute dose and chronic therapy for 3 and 6 months are shown. Note that during chronic therapy suppression of prolactin with both drugs is similar

within 4 hours of administration and remain suppressed for at least 11 hours. Similar observations have been made after a single 0.1 mg dose of lisuride. Figure 1 compares serum prolactin levels in hyperprolactinaemic subjects after bromocriptine and lisuride administration. The normal dose of bromocriptine (2.5 mg three times daily) or lisuride (0.2 mg three times daily) maintains the suppression of prolac-

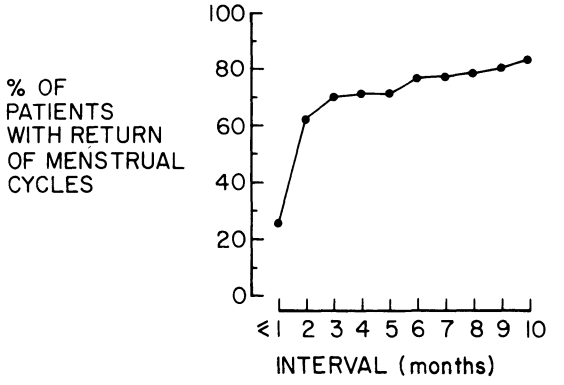

Figure 2 Cumulative percentage of 58 amenorrhoeic hyperprolactinaemic women with return of regular menstrual cycles related to months on bromocriptine therapy. Reproduced with permission from reference 14

tin secretion. Pergolide appears to be longer acting[13]. Figure 2 shows the percentage of amenorrhoeic patients in whom normal menstrual cycles returned plotted against the duration of bromocriptine therapy. It is apparent that within 1 month of initiation of therapy 25% of patients had a return of regular menstrual cycles; within 6 months this percentage rose to greater than 60%; at the end of 10 months 83% had a return of regular menstrual cycles. Of the 17% who did not have a return of normal cycles, all but one patient had previously been treated with either external pituitary irradiation, surgery or both[14]. The result in terms of return of gonadal function is similar in the men. Thus, irrespective of whether the patient has a microadenoma or a macroadenoma the suppression of prolactin, with medical therapy, restores gonadal function in the vast majority of these patients. At the present time bromocriptine, lisuride and pergolide appear to have similar efficacy. Pergolide has the practical advantage that it only needs to be given once daily.

HYPERPROLACTINAEMIA AND PREGNANCY

Many women present with infertility but wish to become pregnant once their ovarian function has been restored. Certain potential problems of pregnancy need recognition. During pregnancy the normal pituitary gland increases in size and it has been observed that some patients with pituitary tumours, meningiomas and other parasellar diseases develop symptoms from growth of these neoplasms during pregnancy. Therefore, the tumour expansion during pregnancy is not a result of the therapy, but instead is intrinsic to the basic disease which is aggravated by the pregnancy.

The incidence of pituitary tumour expansion during pregnancy is unknown. As a rough estimate between 10 and 25% of macroadenomas may enlarge during pregnancy and thus give rise to symptoms. For microadenomas the incidence is probably less than 1% and possibly less than 0.1%[15,16].

Our policy is to discuss thoroughly these risks with our patients and then to recommend to all patients (except those who have pre-existing visual field defects) medical treatment with dopamine agonist drugs. We consider it vital to have excellent baseline neuroradiological and neuro-ophthalmological data before the patient becomes pregnant. This obviates serious management problems if the patient develops symptoms and minor field defects are detected for the first time during pregnancy. The number of women who have large tumours with field defects prior to therapy is very small. In these patients the risks have to be carefully evaluated and the question of surgical decompression of the tumour prior to pregnancy needs serious consideration.

The patients are asked to use mechanical contraception during the early months of therapy, so that they do not become pregnant and their menstrual cycles can be documented. If the patient wishes to become pregnant after three regular menstrual cycles and documentation of a biphasic basal body temperature chart, we advise her to discontinue contraceptive precautions. As soon as a period is 48 hours overdue the dopamine agonist therapy is stopped and a serum β-HCG level is measured. The patient is closely followed up throughout the pregnancy and, if there is any sign of the development of compressive symptoms, the patient is re-started on medical therapy. We do not recommend routinely continuing the dopamine agonist therapy throughout the pregnancy since it is clear that these drugs

cross the placenta and prolactin levels in both the mother and the fetus are suppressed. It is of interest that the amniotic fluid prolactin levels remain extremely high and this presumably reflects production of prolactin by the decidua which is not under dopaminergic control.

Extensive studies have been performed to determine whether there is teratogenic effect of bromocriptine[17]. All studies to date indicate that bromocriptine is safe to use to induce fertility, but the oldest child born to a women who took bromocriptine to induce fertility is now only 10 years old. Therefore, the full development of the children has not yet been documented. The teratogenicity studies of lisuride are discussed in Chapter 3.

MACROADENOMAS SECRETING PROLACTIN

Surgery rarely cures the large prolactin-secreting pituitary adenoma. Patients with pretreatment prolactin levels of greater than 250 ng ml^{-1} or patients with invasive prolactin-secreting pituitary tumours stand less than a 30% chance of being cured by surgery alone[3–5]. An alternative treatment is needed.

The objectives of both medical and surgical treatment are: (1) to reduce the size of the pituitary tumour, particularly if it is producing compressive symptoms; (2) to restore or maintain normal anterior pituitary function; (3) to reduce the serum prolactin level to normal; and (4) to prevent recurrence of the disease. Multicentre studies suggest that some patients with prolactin-secreting pituitary tumours demonstrate rapid improvement in visual fields and resolution of headaches after starting bromocriptine, lisuride, or pergolide therapy[19–27]. This is associated with the reduction of prolactin levels usually by greater than 80% and into the normal range on many occasions. Of greater significance is the improvement of visual field abnormalities in most patients and the radiological evidence of a decrease in tumour size during bromocriptine, lisuride and pergolide therapy. Some investigators advocate medical therapy as primary treatment of patients who present with visual field abnormalities. Indeed the dramatic clinical improvement as a result of reduction in tumour size without the risk of development of hypopituitarism is strong supportive evidence for this recommendation. However, withdrawal of dopamine agonist therapy usually results in a return of hyperprolactinaemia and tumour re-expansion with the attendant risk of visual compromise[25]. In this context, these drugs may be

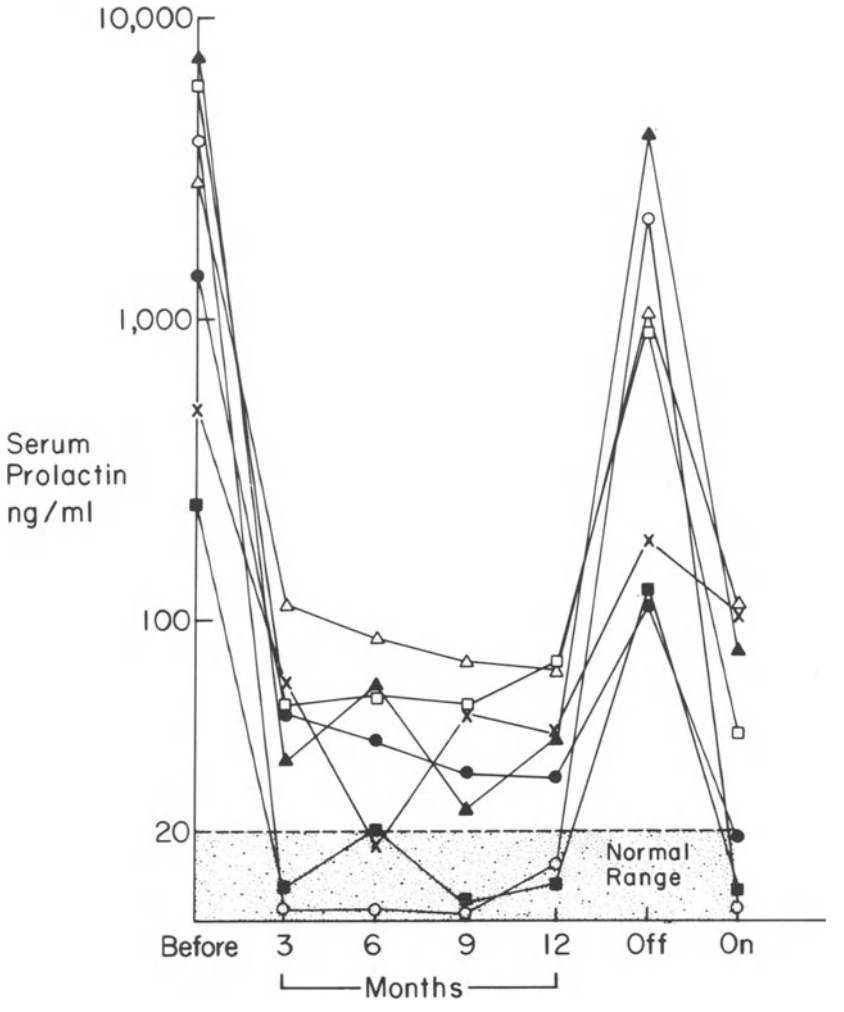

Figure 3 Mean serum prolactin of 10 samples drawn at fixed intervals through the day in seven patients with prolactin-secreting macroadenomas. The results are shown before, at the end of 1 year, after withdrawal, and after re-starting therapy. Note the reduction in the serum prolactin levels during bromocriptine therapy, the increase in the levels when therapy was stopped, and further suppression when therapy was reinitiated. Reproduced with permission from reference 28

viewed as 'replacement' therapy. Thus, a functional dopamine deficiency at the level of the tumour is reversed by dopamine agonists and chronic therapy is required. The size reduction of these tumours can be explained by a reduction in the volume of the individual cells[18]. Diminished cytoplasmic and to a lesser extent nuclear volumes are responsible for these changes. The cell undergoes transformation from an active to a relatively quiescent state with little rough endoplasmic reticulum and decreased nuclear size.

Our major experience has been with bromocriptine. However, in the patients whom we have treated with lisuride the results appear similar. In our series of seven men and six women with hyperprolactinaemia and radiologically documented suprasellar extension, who have had no other antecedent therapy, bromocriptine therapy (2.5mg three times daily) resulted in suppression of serum prolactin levels by 86–99% after 12 months; two of the six men and four of the seven women achieved normal serum prolactin levels. Gonadal function was restored or improved in 12 of the 13 patients. Six of seven women had return of cyclic menses. One woman who had been amenorrhoeic for 16 years has not yet had return of menses; her pretreatment serum prolactin value was $770\,ng\,ml^{-1}$ and decreased to $110\,ng\,ml^{-1}$ after 12 months of therapy. Initially, visual fields were normal in the women and abnormal in five of the six men. After institution of bromocriptine therapy, visual fields improved or became normal in all five men. All patients had a radiologically demonstrated (either by CT scan or pneumocisternography) reduction in tumour size. Bromocriptine was withdrawn in seven patients, and Figure 3 illustrates the changes in serum prolactin level in these seven patients during treatment with, after withdrawal of, and re-institution of bromocriptine. In one patient withdrawal of therapy resulted in return of visual field abnormalities which promptly improved 3 days after re-institution of bromocriptine (Figure 4). Figure 5 shows the changes seen in the CT scans of a woman who was treated for 1 year with bromocriptine. Serum prolactin level decreased from 7340 to $40\,ng\,ml^{-1}$. 6 days after withdrawal of bromocriptine at 1 year the serum prolactin level was $3960\,ng\,ml^{-1}$ and the tumour was clearly larger. Within 8 days of re-starting bromocriptine, the tumour decreased towards the pre-withdrawal size; after 1 month of therapy the serum prolactin value was $77\,ng\,ml^{-1}$.

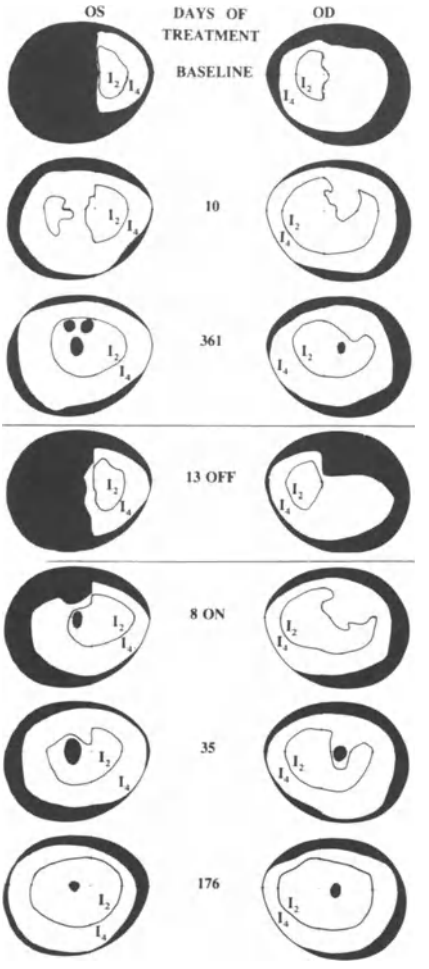

Figure 4 Diagrammatic representation of visual field plot in a 24-year-old man before, during, after withdrawal, and after reinstitution of bromocriptine therapy. The visual fields were plotted using the Goldmann apparatus under light intensive, 1000 apostilb (I_4) and 100 apostilb (I_2). The black periphery indicates a normal visual field for comparison. Before therapy (baseline) a bitemporal hemianopsia, complete in the left eye and incomplete in the right eye, was present. The visual fields were greatly improved at 10 days, and only an equivocal superior bitemporal quadrantic defect to the low intensity object was present on the 361st day. On the 13th day after withdrawal of medical therapy, the field defects recurred; an almost complete temporal hemianopsia in the left eye and an incomplete temporal hemianopsia in the right eye were present. Progressive improvement in the visual fields was again observed over 6 months after reintroduction of therapy. Reproduced with permission from reference 25

CONCLUSIONS

Hyperprolactinaemia is an important cause of infertility in women. Its recognition in an individual patient is important since specific, simple, and reliable therapy is available with dopamine agonist drugs. Problems of potential pituitary tumour expansion during pregnancy exist but are minor in patients with microadenomas, who make up greater than 80% of such patients. The recognition of the hyperprolactinaemic syndromes and the advent of dopamine agonist drugs offer a major advance in the treatment of infertility.

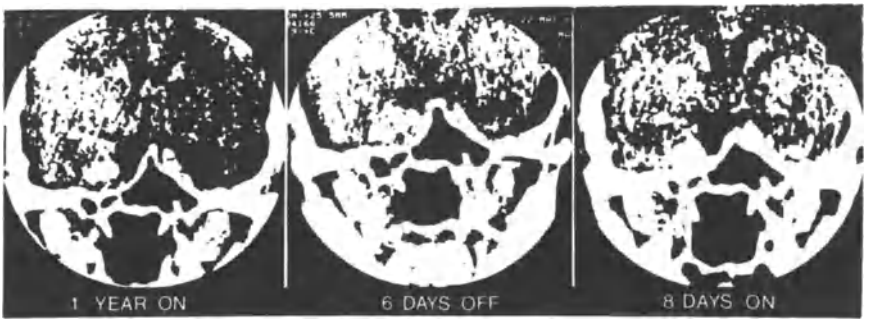

Figure 5 Coronal sections of CT scan through the sella turcica; at 1 year of bromocriptine treatment (left) in a young woman with a prolactin-secreting macroadenoma. There is a partially empty fossa and some residual tumour in the cavernous sinus. 6 days after bromocriptine withdrawal (centre) the tumour has re-expanded to fill the pituitary fossa, and 8 days after re-starting therapy (right) the tumour size had decreased towards the pre-withdrawal value. Reproduced with permission from reference 28

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3
Lisuride – a new drug for treatment of hyperprolactinaemic disorders

R. HOROWSKI, R. DOROW, A. SCHOLZ, L. DE CECCO and W. H. F. SCHNEIDER

SUMMARY

Lisuride (Dopergin®), a highly active dopaminergic ergot derivative with prolactin-lowering properties, has an outstanding affinity as an agonist for dopamine receptors. It is concentrated by a factor of 5–10 above lisuride plasma levels within the pituitary where it acts on dopamine receptors which inhibit prolactin release. In rats, oral lisuride is 10–30 times more active on a weight basis as a prolactin-lowering agent than bromocriptine. In carcinogenicity studies in rodents, no endometrial carcinomas could be found after 2 years of treatment; on the contrary, development of pituitary tumours was prevented almost completely and there was a dose-dependent reduction in the incidence of mammary tumours. Studies in rats, rabbits and monkeys revealed no teratogenic potential of the drug. On acute administration, doses as low as 0.1 mg of lisuride p.o. decrease prolactin plasma levels in humans; this effect is enhanced and prolongated on repeated administration. Its effect is highly specific and no other hormonal systems are affected with the exception of growth hormone. Lisuride can be used in all clinical conditions where a dopaminergic or prolactin-lowering effect is needed, and its activity is unsurpassed by any other form of treatment. In the prevention of post-partum lactation, controlled studies point to a lower incidence

of rebound lactation than observed with other treatments. Lisuride effectively restores normal cycles and fertility in hyperprolactinaemic women. In the pregnancies documented so far, which were induced by lisuride treatment, no evidence for any particular abnormality was observed. In healthy males, lisuride treatment did not affect spermatogenesis. In hyperprolactinaemic men suffering from prolactin-producing tumours, testosterone synthesis as well as libido, potency and fertility can be restored with lisuride. In the case of macroprolactinomas, treatment with lisuride not only lowered prolactin levels but also led to a sometimes dramatic reduction of tumour volume.

All these data suggest that lisuride is a highly effective drug in the treatment of menstrual cycle and fertility disorders and related situations, and a valuable alternative to bromocriptine.

Lisuride (Dopergin®; 8-(9,10-didehydro-6-methyl-ergolin-8α-yl)-1,1-diethyl-urea hydrogen maleate; Figure 1) is a semi-synthetic ergot derivative with an outstanding affinity for central monoamine receptors.

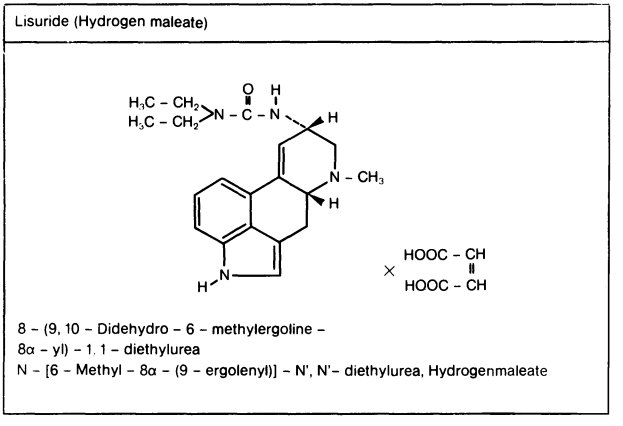

Figure 1 The structure of lisuride

In numerous pharmacological experiments lisuride has been shown to be a potent direct dopamine agonist as well as a serotonin partial agonist[1–3]; at much higher dosages, it has also α-adrenolytic

and even β-receptor blocking activity (Table 1). In biochemical *in vitro* and *in vivo* investigations lisuride has been shown to be one of the most potent dopamine receptor agonists. The compound displays a very high affinity for D_1 and D_2 dopamine receptors as well as for 5-HT_1 and 5-HT_2 receptors[4,5].

Table 1 Pharmacological profile of lisuride

LOW DOSES	
High-affinity binding to serotonin (5-HT_1 and 5-HT_2) receptors	
Functional inhibition of serotoninergic neurones of raphe dorsalis and inhibition of peripheral effects of serotonin	Prevention of migraine attacks (daily dose 0.075 mg by mouth)
High-affinity binding to dopamine receptors of the anterior pituitary	
Inhibition of prolactin release (acute effect) and synthesis	Prevention of lactation, treatment of galactorrhoea, amenorrhoea and other cycle and fertility disorders (daily dose 0.4–4 mg by mouth)
INTERMEDIATE DOSES	
High-affinity binding to dopamine receptors of the striatum	
Postsynaptic activation of dopamine receptors (particularly in supersensitive states, e.g. dopamine-depleted animals)	Treatment of Parkinsonism and related diseases (daily dose 0.6–10 mg by mouth)
HIGH DOSES	
Binding to α- and β-receptors	
α-adrenolytic and β-blocking effects	No clinical correlations

When given to rats, dosages in the microgram range inhibit the firing rate of raphe dorsalis neurones – an effect that seems to be due to an activation of 5-HT autoreceptors which results in a functional inhibition of serotonin effects[6]. The interaction of lisuride with serotoninergic systems is believed to be the pharmacological basis for the high efficacy of lisuride in the prevention of migraine attacks[7].

Doses of lisuride in a similar range reduce reserpine-induced rigidity and, at higher doses, also akinesia and hypothermia[8,9]. In rats that were not pretreated with reserpine, lisuride inhibited the neuronal firing rate of dopaminergic neurones in the substantia

nigra[6]. This phenomenon is interpreted as being due to a negative feedback mechanism as a consequence of the stimulation of dopamine receptors by lisuride. The very potent dopamine agonist activity of lisuride in these systems is the basis for the use of this drug in the treatment of Parkinson's disease, which is defined by a deficit of dopamine in the nigroneostriatal pathway[10].

The unique combination of dopaminergic activity and functional serotonin antagonism is the cause of the occurrence of pronounced, stereotyped and long-lasting mounting behaviour which can be observed in rats treated with high doses of lisuride. This behavioural phenomenon which mimics male sexual activity seems to be independent from the hormonal situation of the animals because it can be produced also in female, juvenile or castrated animals[11]. In castrated male rats, lisuride restores in a dose-dependent way not only mounting behaviour, but also penile erection, intromission and ejaculation. These effects confirm that in rats, sexual activity can be restored or enhanced by a combination of serotonin antagonistic and dopaminergic activity[12].

Since dopamine plays a crucial role in preventing prolactin release from anterior pituitary prolactin cells, it is not surprising that extremely low oral doses of lisuride 10 μg (kg body weight)$^{-1}$ significantly lower serum prolactin levels in rats. In this respect, lisuride is at least 10 times more active than bromocriptine. Amongst all dopamine agonists used clinically lisuride has the highest affinity for dopamine

Table 2 Competition by various agents for [^{3}H]-spiperone binding to 7315a pituitary tumour*

Agonist	K_i (*nmol l^{-1}*)†
Lisuride	0.39±0.18
Bromocriptine	10±4
Pergolide	45±7
6,7-ADTN	236±66
Apomorphine	250±70
DA	2 900±1 200
1-Epinephrine	17 000±1 000
1-Norepinephrine	29 000±8 000
Serotonin	83 000±30 000

*Modified from reference 13.
†Means ±SE.

receptors located on pituitary prolactin cells (Table 2). Furthermore,

lisuride prevents prolactin-dependent function in rats, such as lactation, mammary development and luteolysis[14]. In carcinogenicity studies where female rats and mice were treated with various doses of lisuride over a period of 2 years, lisuride prevented in a dose-dependent way the development of pituitary and mammary tumours

Table 3 Tumour incidence (%) in female rats treated with lisuride for 104 weeks*

Dosage ($mg\,kg^{-1}$ *by mouth)*	*Surviving animals (n)*	*Mammary adenomas*	*All pituitary tumours*	*(males)*
Controls	29	32	48	(40)
0.02	39†	16	49	(18)†
0.2	44†	6†	12†	(16)†
1.0	39†	2†	4†	(10)†

*From G. Schuppler (personal communication).
†Difference between control value and incidence significant at $p \leq 0.05$
Also dose-dependent decrease in tumour incidence: adrenal tumours (phaeochromocytomas and cortical adenomas) and thyroid C-cell adenomas.
There was no significant increase in tumour incidence (in particular no increase in endometrial tumours).

(Table 3) as well as of tumours of other organs (G. Schuppler, personal communication). No increase in the number of endometrial tumours was observed in the lisuride studies. In these as well as in other studies, where the development of pituitary tumours was prevented by treatment with lisuride the life-span of the animals was increased.

Extensive studies in rodents and monkeys failed to give any evidence of a teratogenic effect; lisuride was embryotoxic only at doses where also some of the adult animals died. The compound crosses the blood–placenta barrier and the blood–brain barrier and seems to achieve higher levels in brain areas with larger numbers of dopamine receptors. In the pituitary, its target organ, radioactivity after treatment with [^{3}H]lisuride is 5–10 times higher than in the blood. This accumulation may be the reason why the prolactin-lowering effect of lisuride is enhanced on repeated administration[15].

In humans lisuride is completely absorbed but undergoes, like most ergots including bromocriptine, a variable first-pass effect. Prolactin-lowering activity does not seem to correlate with lisuride plasma levels as measured by specific RIA but side-effects seem to be

more likely with higher concentrations in the blood. The variability in plasma levels may be the reason why – again as with other ergots – the dosage needs to be adjusted individually in all indications except prevention of postpartum lactation (where dopamine agonists are tolerated particularly well, possibly because of altered pharmacokinetics or to a cross-tolerance with oestrogens as regards nausea and other side-effects).

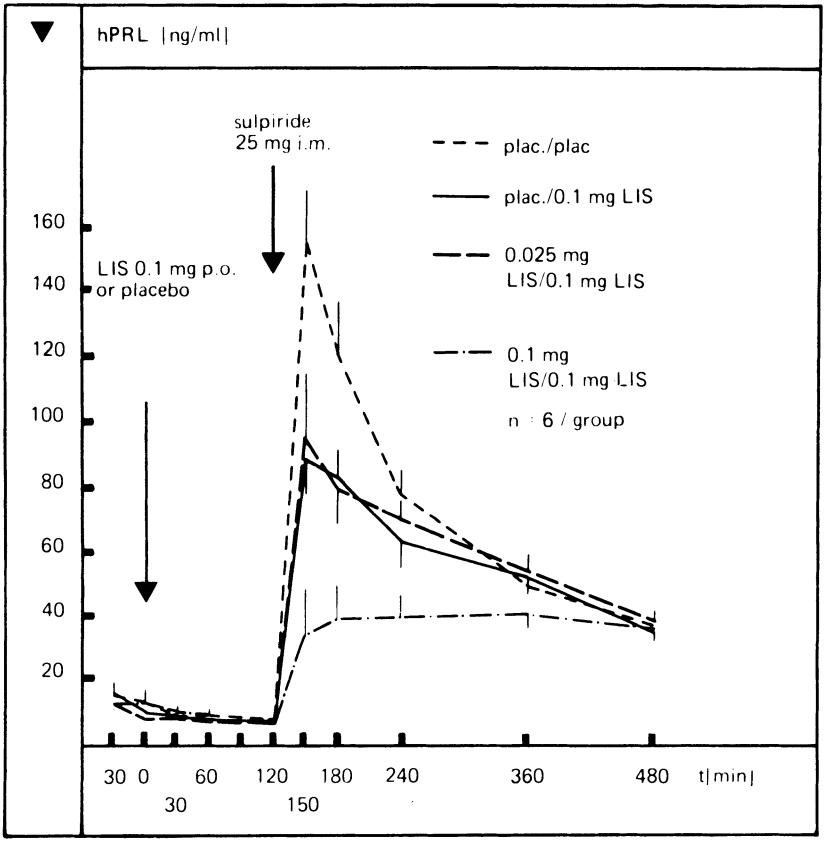

Figure 2 Influence of treatment for 2 weeks with placebo, 0.025 mg lisuride (LIS) three times daily or 0.1 mg lisuride three times daily on the acute effect of 0.1 mg lisuride on sulpiride-induced hyperprolactinaemia in healthy female volunteers. From reference 15

Lisuride is excreted from plasma and has a half-life of 2–3 hours[16]. Again, there is no correlation with its effects on prolactin levels which are lowered by a single dose of lisuride for 8–12 hours. This

observation points again to a pituitary accumulation, as well as the observation that the prolactin-lowering effect is clearly enhanced on repeated administration (Figure 2), and plasma prolactin levels remain low for days or even weeks after cessation of treatment in patients with prolactin-producing adenomas. The prolactin-lowering effect of lisuride is dose and time dependent. A dose of 0.2 mg lisuride is equipotent to a dose of 2.5 mg bromocriptine. Similar dose-dependent effects were observed in the inhibition of postpartum lactation: whilst 3 × 0.05 mg failed to be better than placebo, 3 × 0.1, 3 × 0.2 and 3 × 0.3 mg daily lowered prolactin and prevented lactation in postpartum women in a dose-dependent way[17]. In two controlled comparative studies *vs.* bromocriptine, similar clinical effects could be achieved by doses of 0.2 mg lisuride and 2.5 mg bromocriptine; in both studies, however, there was less rebound lactation after a fortnight's duration of treatment in the lisuride group[18,19] (Table 4). This difference, too, can be interpreted in terms of a higher affinity of lisuride for dopamine receptors within the pituitary and its accumulation there.

Treatment with dopamine agonists has been shown recently to be very useful also in lactating women with beginning or fully established mastitis. By reducing the breast congestion immediately after application, it is even possible in some cases to avoid use of antibiotics and to maintain breast feeding.

Dopamine agonists are also able to inhibit galactorrhoea, whether associated with elevated prolactin levels or not, and they can also effectively reduce mastodynia and other symptoms of pathological forms of the so-called premenstrual syndrome, as shown for lisuride in one extensive controlled double-blind study using 2 × 0.1 mg daily[20]. Beneficial effects of this treatment on psychic and EEG alterations in this syndrome are possibly not caused by the prolactin-lowering effect of this compound, but may also reflect interaction with other dopaminergic or serotoninergic systems in the brain, as is the case in the preventive treatment of migraine with lisuride[7]. It may be relevant that this condition is often influenced by hormonal changes and can occur during the premenstrual phase.

It is still unclear whether prolactin-lowering drugs are also of clinical use in other breast diseases, e.g. cystic mastopathy, or whether even the incidence of mammary tumours might be reduced by long-term treatment with those compounds, as has been observed in animal studies.

Table 4 Overall clinical evaluation of effects of bromocriptine and lisuride on sulpiride-induced hyperprolactinaemia[†]

	Lisuride							*Bromocriptine*					
Patient No.	*Secretion*		*Congestion*		*Pain*			*Patient No.*	*Secretion*		*Congestion*		*Pain*	
	*A**	*B***	*A*	*B*	*A*	*B*			*A*	*B*	*A*	*B*	*A*	*B*
1	0	0	0	1	0	0		2	3	2	4	2	3	1
3	2	1	0	0	0	0		6	4	0	0	0	0	0
4	0	0	0	0	0	0		9	0	0	0	0	0	0
5	0	0	0	0	0	0		13	0	0	1	0	0	0
7	0	0	1	0	1	0		14	Dropped out – dizzyness on day 10					
8	0	0	0	0	0	0		16	0	0	0	0	0	0
10	0	0	0	0	0	0		17	0	2	0	2	0	0
11	0	0	0	0	0	0		20	0	0	0	0	0	0
12	Dropped out – dizzyness on day 10							21	0	0	0	0	0	0
15	2	1	4	1	2	1		24	0	5	0	4	0	4
18	0	0	0	0	0	0		25	Dropped out – headache on day 10					
19	0	0	0	0	0	0		27	0	0	0	0	0	0
22	0	0	0	0	0	0		30	0	0	0	0	0	0
23	10	0	0	0	0	0		32	0	4	0	3	0	3
26	0	0	1	0	0	0		34	0	0	0	0	0	0
28	0	0	1	1	0	0		35	0	0	2	0	0	0
29	4	0	2	0	0	0		36	Dropped out – stomach ache on day 6					
31	0	0	0	0	0	0		39	0	0	0	0	0	0
33	0	0	0	0	0	0		40	3	6	3	6	3	6
37	2	0	2	0	2	0		41	2	0	1	1	0	0
38	0	0	0	0	0	0		42	0	0	0	0	0	0
Total	20	2	11	3	5	1			12	19	11	18	6	14

*A is the sum of the scores for the first 15 days (treatment).
**B is the sum of the scores for the last 10 days (rebound).

Score	*Milk secretion*	*Congestion*	*Pain*
0	No milk	None	None
1	Few drops on expression	Mildly or slightly indurated	Mild
2	Abundant on manual expression	Moderately indurated	Moderate
3	Spontaneous stream of milk	Severe	Severe, requiring analgesics

[†]From reference 19.

According to its direct effect on the prolactin-producing cell, lisuride can lower prolactin levels in all situations, and thereby change or restore biological function. Elevated prolactin levels in women may cause anovulation, premenstrual symptoms, short luteal phases or, at higher levels, amenorrhoea with or without associated galactorrhoea. Prolactin may influence steroid production at the gonadal level, but the most important mechanism by which elevated prolactin levels inhibit gonadal function seems to be due to a change in the pulsatile LHRH secretion from the hypothalamus possibly associated with an altered dopamine turnover. This can be demonstrated by the observation that pulsatile administration of exogenous LHRH is able to restore normal ovulatory cycles and thereby achieves pregnancies even in the presence of greatly elevated prolactin levels. A similar result, however, can better be obtained by lowering elevated prolactin levels using dopamine agonists such as lisuride. Here, within months, normal menstrual cycles and thus pregnancies can be ob-

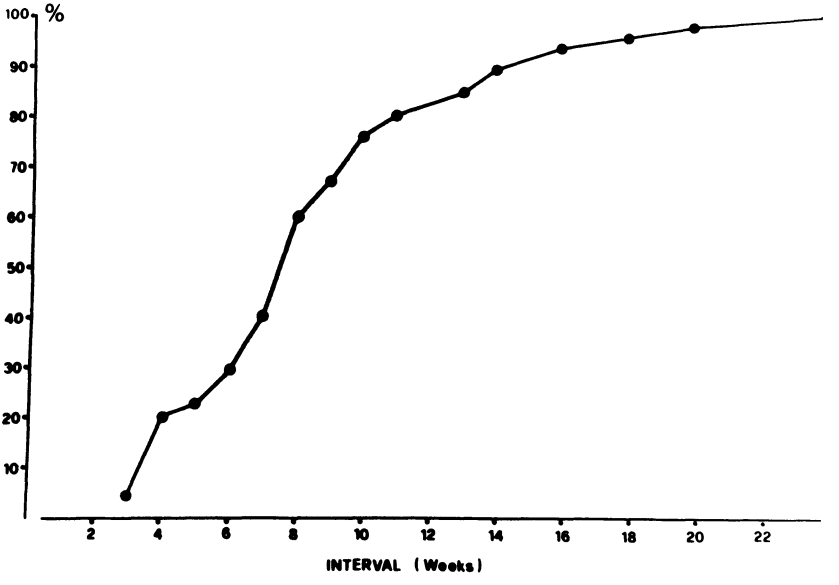

Figure 3 Percentage of 45 amenorrhoeic, hyperprolactinaemic women with return of regular cycles relative to weeks of lisuride treatment. From reference 19

tained (Figure 3)[19]. Owing to the high specificity of lisuride for dopamine receptors, no other hormones are affected by treatment with it.

In the treatment of hyperprolactinaemic disorders, one can expect higher prolactin levels (above 100 and particularly above 500 ng ml^{-1}) to be caused by larger pituitary adenomas, which, as a rule, need higher doses of lisuride. Since there are, however, exceptions, and since bioavailability of dopamine agonists varies sometimes considerably, it has become clinical practice to start with low, slowly increasing doses which are given at meals (this also helps to avoid initial side-effects such as nausea) and preferentially in the evening in order to minimize risks caused by orthostatic hypotension which, if it occurs, most often is seen only once after the first effective dosage. If with the standard daily dose of 2–3 × 0.2 mg no sufficient effect on symptomatology and prolactin levels has been achieved, the dosage can be increased at weekly to monthly intervals until prolactin levels and biological function are normalized. Daily doses of lisuride as high as 5.0 mg may be necessary in rare cases of pituitary macroadenomas.

However, in spite of the high success rate of treatment with dopamine agonists in hyperprolactinaemic disorders, treatment should not be started at once when elevated prolactin levels have been detected. A differential diagnosis is necessary which may rule out physiological causes (including lactation, stress, etc.) or, for example, hypothyroidism. In this disease, low peripheral thyroxin levels can result in an enhanced TRH function which not only acts on TSH but also releases prolactin from the anterior pituitary. This type of hyperprolactinaemia, therefore, responds well to thyroid hormone substitution therapy. In addition, drugs that are known to increase prolactin levels (such as metoclopramide, sulpiride, neuroleptics, cimetidine, reserpine and α-methyl-dopa) must be identified and, if possible, withdrawn. Great care must be taken in identifying a pituitary tumour as the cause of hyperprolactinaemia by use of a skull X-ray and, if necessary, CAT scanning. Even if most experts today agree that medical treatment with the dopamine agonists bromocriptine or lisuride is the treatment of choice, there are rare but well-documented cases in the literature where a pregnancy with high oestrogen levels has caused a considerable increase of some of these tumours resulting even in blindness or death. Therefore, particular care has to be taken in women who desire to become pregnant and who have evidence of large adenomas. Monthly visual field examination and prolactin measurements are necessary during pregnancy and women should be advised to refer to a hospital at the

earliest clinical signs indicating re-growth of a tumour (e.g. headaches and visual disturbances), in order to undergo medical treatment or neurosurgical intervention.

No such events, however, have been seen in the more than 100 pregnancies induced by lisuride treatment. Similarly, no adverse effects of lisuride on pregnancy development and outcome have been observed, and particularly no malformations have been reported so

Table 5 Outcome of 118 pregnancies obtained by treatment with lisuride*

Early abortion	21 (17.8%)
Tubal pregnancy	1
Healthy infants	97

*Data on file (Schering).
There were no malformations and the sex ratio was normal.

far (Table 5). Although this number is still too low to draw definite conclusions from, the likelihood of an increased risk is already very low, and the results of the animal studies with lisuride as well as the experience obtained with bromocriptine as the other prolactin-lowering drug of ergot structure seem reassuring. The relatively high percentage of stillbirths observed in our consecutive 118 pregnancies seems to be not too unusual in women with fertility problems, particularly if one considers that treatment with lisuride was, for many of them, a last chance.

Whilst oestrogens rarely may enhance tumour growth, dopamine agonists have been reported to reduce the volume of macroprolactinomas in a high percentage of cases treated; in agreement with this, and also in confirming animal data as reported above, chronic treatment with lisuride has been shown to lower prolactin levels in patients with pituitary tumours and to restore normal ovulatory cycles, or, in males, libido and potency[21]; clear evidence for tumour shrinkage has also been obtained[22]. It has therefore been proposed to use medical treatment by dopamine agonists in patients with prolactin-producing tumours. However, if neurosurgery is to be performed, pretreatment with lisuride or bromocriptine is quite helpful and seems to improve the results of surgery. In these as in other conditions, the use of intravenous lisuride may be of value both for treatment and for diagnosis.

In conclusion, lisuride is the most potent dopamine agonist for clinical use that can be used as a prolactin-lowering compound whenever prolactin is involved in the pathophysiology of symptoms and diseases. It is well tolerated and no particular toxicity has been reported. Lisuride (Dopergin) thus can be used as an effective and safe prolactin-lowering and dopamine agonist drug.

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4
Benefits and risks of hormonal contraception – interpretation

M. SMITH

ABSTRACT

The pill is undoubtedly one of the greatest and most efficient of medical advances. In 1976 in the UK 3.5 million women took the pill but following adverse publicity linked to often misinterpreted findings of the report from the RCGP this number decreased by 600 000. Caution should certainly be taken in those over 35 years who smoke but general acceptance of all possible side-effects without informed interpretation is not in the best interests of patients. Happily, recent advances in pill dosage and formulation together with follow-up studies from the RCGP, have suggested there is no new overall increased risk in the long term and that there may be benefits due to the pill decreasing the incidence of benign breast disease, cancer, cysts of the ovary and PID. From the low level of up-take of 2.8 million in 1979, by 1982 approximately 3.3 million in the UK are again taking the pill. The lost 500 000 have returned and it is likely that 3.35 million women will be taking it in 1983. This trend can, however, only continue where there is a forward looking family planning service particularly among the young and deprived. Patients must be actively sought out and walk-in service for all methods currently used must be provided. We must continue to restore confidence in the pill as we are unlikely to have anything better as a contraceptive agent if at all until the next century.

In the relatively minor controversies that occur concerning what must undoubtedly be one of the greatest medical advances ever – the birth pill – it is the daily practice of clinicians on being consulted by women taking the pill that provides clinicians with their confidence in the method.

We should never forget that interpretation is the key word that may be vital for the well-being of our patients. It is the clinicians who put the latest scientific report into perspective.

The pill is a topical subject. In my office at home, in the space of a few months, photocopies of articles written both 'for' but slightly more often 'against' the pill and other birth-control methods that have appeared in the national and local press and women's magazines have produced a pile, inches high. To read some of the more sensational articles gives me cause to wonder whether the writer has discovered new methods, since they often do not sound like those used by the vast majority of people that I deal with; but they are. The writer's interpretation, however, is different.

The fact is that the pill is probably the most efficient medicine we have ever known. That is easy to interpret. It is virtually 100% effective in preventing pregnancy, but this rarely gets mentioned.

The often finer effects of the pill that are discussed in the following chapters are based on the author's precise scientific research and observations. The interpretation of these results and their practical effect, or the lack of it upon women, needs to be interpreted by others with specialist knowledge – both epidemiological and practical.

Later chapters will be describing the effect that the pill has upon the levels of fat in a woman's blood. It will be explained, where relevant, that most often what we are really dealing with is the significance of these biochemical findings.

If misinterpreted, these findings can have an unnecessary and alarming effect upon the confidence of the users, not to mention the destruction it may cause to their personal relationships. It may lead them to change from one method to another, away from the one they really want to use, to a method that they may not be motivated towards and will therefore use less effectively, with possibly disastrous results in terms of an unwanted pregnancy at worst, and at best a lessening in the quality of their lives.

To see the magnitude of such effects I would like to point out a few basic facts. In retrospect, the cause and effect seem obvious though the details will always be open to discussion. In 1976 there

were in the United Kingdom 3½ million women taking the pill. In 1977 a respected body of researchers from the Royal College of General Practitioners published a report, the most notable and practical conclusions of which were that the excess mortality due to the pill increased with age, cigarette smoking and duration of pill usage. By 1979 there were 600 000 fewer women taking the pill. I remember that, together with colleagues from the Family Planning Association, I did some sums at the time and concluded that if women over 35 years of age alone had been advised to take heed of the signposts to safer pill taking that the RCG Report offered, then almost one half of the women who fled from the pill having had their confidence shaken need not have done so. There were only some 350 000 women at most who were taking the pill and who were over 35. If personal symptoms suffered were the reasons why the others stopped taking the pill, then it is understandable that the women would want to change. But as those of us with chemical experience know, those symptoms, too, vary with the confidence that a women has in her chosen method. Caution on the part of the doctor prescribing for those who are over 35 and who smoke is the main and justifiable inference to be taken from those RCGP findings which were published in a journal aimed at the medical profession, the *Lancet*. In medical affairs, such statistically based facts will usually require personal articulation for the person most concerned – the patient – if she is to be best served. A general acceptance of facts, without informed interpretation, will not be in the best interests of a minority of patients.

One small but definite example of my message is presented in the *Lancet* on October 30th 1982, again by the RCGP, based on their oral contraceptive study. In summary it reads 'previous studies of gall bladder disease provided strong evidence of increased incidence associated with the use of oral contraceptives.' This present study suggests that there is no overall increased risk in the long term and that the previously demonstrated disease occurs *only* in women who are susceptible to it. The acceleration may be associated with the dose of oestrogen in the oral contraceptive. It is perhaps unfortunate that women who would be happy to take the pill were it not for the diminished confidence medical reports can induce when they are given inappropriate publicity, regard themselves as unhappy contraceptors. They are worried women, or worse still they are forced, unwantedly, into motherhood. In both instances it is more often the other methods of contraception that wrongly get the blame. The

woman is understandably less happy with them than she would be with the method she really wants to use. The wisest interpretation of that report might have been to follow the implied advice in favour of using the lowest effective dose.

But what about the benefits of the pill? I am going to expand a little on a few of them and largely quote from an article by Howard Ory – the epidemiologist – in the July/August 1982 issue of *Family Planning Perspectives*. He points out that in the United States alone 50 000 hospital admissions are prevented each year due to the beneficial effects the pill has on women taking it. Benign breast diseases are prevented as well as cancer that would otherwise have occurred in the reproductive systems of those women. 50 000 women: if only those individuals were able to know that it was the pill that could have saved them surgery, we might be witnessing a rise in pro-pill pressure groups!

Those of us who have seen the anxieties caused to women with a breast lump in the days they have to wait to consult a surgeon, with the fear of an operation heavy on their minds, can take heart from the fact that of those of our patients who are on the pill, three out of four will not have to suffer that experience.

Cysts of the ovary, too, are affected beneficially by taking the pill, reducing again the need for surgical operations that would otherwise have been necessary. It is estimated that some 3000 such operations are prevented in the United States each year among women who are taking the pill. Further, pill-users have only half the chance of suffering from anaemia, as well as pelvic inflammatory disease which causes pelvic pain and often continual suffering. The pill may prevent pelvic inflammatory disease in two out of three women who would otherwise get it.

The low-dose pills including the pill with three different dose phases throughout a woman's cycle – the triphasics – together with others first introduced around 1980 allow a woman, these days, to take in a whole month less hormone than she would have taken in a day 20 or more years ago and still afford almost 100% protection against pregnancy. A 95% reduction in dosage while still maintaining efficiency; I find that quite amazing.

The outcome of much misinterpretation about the scientific data on the pill has happily not influenced the pill-taking habits of the bulk of the women in the UK for too long. They have been flocking in their hundreds of thousands back to the pill. From the low level

of uptake, 2.8 million women in 1979, and with the introduction and rapidly growing popularity of triphasic pills in 1980 as well as other low-dosed pills, we are now able to see that about 3.3 million women have again taken the pill during 1982. The lost 500 000 have returned. It is likely that 3 350 000 women will be taking it in 1983, another 50 000.

On behalf of our patients, what we ask of our research colleagues is that in the more open medical climate in which we now live, we all work towards communicating clearly those results that justifiably call for a change in practice, noting specifically, for instance, that the older woman who smokes is especially at risk, so that we can try to protect her from the harm that her smoking habit may cause.

The real risks of not taking the pill when nothing else is acceptable is of course the risk of an unwanted pregnancy. This single risk can make biochemical discussions like those given in the rest of this book, which enlarge upon the potential, theoretical, risks of taking the pill, seem so thin as not to be in the same league at all.

In April last year the Chairman of the Family Planning Association, John Dunwoody, himself a general practitioner as well as being a Chairman of a Health Authority, wrote to all the chairmen of the health authorities and pointed out that despite very marked improvements in the introduction of free family planning, there is still a long way to go. And this is in the UK where we don't face the cultural difficulties of our colleagues in Ireland.

High levels of unwanted pregnancies and abortions continue to be acknowledged as a severe problem. The huge costs of unwanted social and other services including education and housing are often hidden and therefore generally unacknowledged. None the less, with an estimated 200 000 unwanted pregnancies annually in the UK spread across some 300 health authorities, financial as well as health implications for each district cannot be ignored. In particular it is among the young and the deprived that a forward-looking family planning service can do most to help prevent the unwanted pregnancies and abortions that otherwise follow. Recent US research shows that family planning provision can save twice its cost in related health and welfare services every year.

The advantages of providing a contraceptive service are well covered in a series of articles published between October 1981 and October 1982 in the *British Journal of Family Planning.*

Dr Moulds, from general practice in the UK points out that the

NHS family planning service is mainly attracting patients who are highly motivated. He believes it will not be a successful service until it attracts a considerable proportion of those who are at present unmotivated. He suggests that as well as providing a comprehensive and up-to-date family planning service, a general practitioner must actively seek out patients. From the consumer point of view it is a walk-in service rather than an appointment system that attracts them to the clinics in preference to the modern-day general practice surgery. Obviously, women with unwanted conceptions will frequently be referred to hospital, so it is vitally important perhaps that there the first opportunity for a discussion about contraception with a doctor who is motivated and well versed in the subject should be available.

My main plea is that we should continue to restore confidence in the pill, the greatest method of contraception we have ever had. We are most unlikely to have anything appreciably better, if at all, before the next century. Confidence should be expressed also in the other methods currently used. Motivation, that most important aspect of contraception, needs to exist amongst the professionals and other staff themselves and be passed on to the user. In recent years Governments have constantly put forward the philosophy that prevention is better than cure. A case can be made that family planning is fundamental to preventive medicine and is the foundation upon which any health programme will rest if it is to succeed.

5
Towards safer oral contraception

C. R. KAY

ABSTRACT

The large size of the Royal College of General Practitioners' Oral Contraception Study enables the risk to users to be estimated with increased precision. It is now clear that non-smokers may safely use oral contraceptives beyond the age of 40 years, especially if brands with low-progestogen activity are prescribed. There is no longer convincing evidence that duration of use contributes materially to the risk. However, for cigarette smokers it would normally be unwise to continue use after the age of 35 years, unless they stop smoking.

Recent publications from the Royal College of General Practitioners' Oral Contraception Study have analysed the association of oral contraceptive (OC) usage with vascular diseases – both total[1] and fatal[2]. These data support and extend similar observations from other studies[3].

All analyses show that the risk is substantially confined to cigarette smokers over the age of 35 years. Thus, in the age group 35–44 years the excess mortality risk is 1 in 2000 users each year in smokers (a statistically significant excess) while in non-smokers the risk is much less at 1 in 6700 users per annum, and this estimate does not differ significantly from the risk in non-pill users.

Unlike previous analyses of mortality published in 1977[4], there is now no evidence of a relationship to duration of use. There is a

suggestion from the mortality data that the increased risk of vascular disease may persist after OCs have been stopped. The analyses of total incidence of arterial disease show that this apparent risk in former users is confined to cerebrovascular disease and that the increased occurrence persists for at least 6 years. However, the risk is small and since it has not been observed in other studies it must be regarded as a hypothesis that requires confirmation. There is also weak evidence that the occurrence of cerebrovascular disease in OC users may be related to duration of use, but the trend is not statistically significant and also requires confirmation in other studies. The study was unable to confirm the observation of Slone and colleagues[5] that the risk of myocardial infarction was related to duration of OC use.

Because relative risks of vascular disease mortality in OC users were generally higher than for vascular disease incidence, there is an implication that case-fatality rates may be higher in OC users. This was shown to be true, but is entirely due to the high case-fatality rate in OC users who smoke cigarettes. This rate is double that in OC users who do not smoke, and in non-OC users whether they smoke or not. This further demonstrates the crucial influence of cigarette smoking on the safety of oral contraception.

All these estimates of risk are based on a population of women who have used a wide range of OCs, many containing higher doses of steroids than are currently used. The demonstration of the progestogen dose dependency of the risk of arterial disease associated with OC usage[6–10] means that if brands are used with a low level of progestogen activity, the risks are likely to be materially lower. Thus, the use of low-dose progestogen brands and the careful exclusion from oral contraception of the small minority of women who have an increased risk of vascular disease will allow the great majority of women to use the pill with remarkable safety.

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6
The influence of the triphasic pill and a desogestrel-containing combination pill on some physical, biochemical and hormonal parameters: a preliminary report

C. P. Th. SCHIJF, C. M. G. THOMAS, P. N. M. DEMACKER, W. H. DOESBURG and R. ROLLAND

SUMMARY

The triphasic pill contains the lowest dose of progestogens given per cycle. The recently introduced desogestrel-containing combination pill is claimed to have less androgenic side-effects than combination pills containing levonorgestrel. A better comparison would be between the triphasic pill and the desogestrel-containing pill. This is the purpose of this report. The following items were measured during the follicular and luteal phase of a control cycle and during the third week of pill intake of both the third and sixth pill cycle: body-weight, blood pressure, total cholesterol, HDL-cholesterol, fasting triglycerides and testosterone. Blood glucose and insulin levels were measured during a glucose tolerance test at the beginning and the end of the study. Body-weight increased and blood pressure remained unchanged during the control cycle. Both pill types had no influence on these parameters. Total cholesterol, HDL-cholesterol and fasting triglycerides showed no significant changes during the control cycle

or during pill intake except for a significant decrease of total cholesterol in the desogestrel group. The triphasic pill did not alter the glucose or insulin response to glucose. In the desogestrel group both these responses increased significantly. Testosterone increased significantly during the control cycle but no significant changes were observed during pill intake in both groups. It is concluded that the observed changes in biochemical and hormonal parameters are minor and only reach the level of significance in the desogestrel group.

INTRODUCTION

Since the introduction of oral contraceptives continuous efforts have been made to reduce both the oestrogen and progestogen content per pill. Also, more specific progestogens have been introduced like levonorgestrel. A drawback of the low-dose oral contraceptives has been the decreased cycle control, with increased intermenstrual bleeding.

The recently introduced triphasic formula with 40% less levonorgestrel as compared with sub-50 oral contraceptives containing this progestogen does not have this disadvantage: despite the low dose of progestogens its cycle control and overall tolerance are excellent[1].

In 1981 Marvelon was introduced. This sub-50 oral contraceptive contains desogestrel – a new progestogen, which has been claimed to be a more specific progestogen than levonorgestrel with less androgenic residual effects[2].

From the data presented so far it can be questioned whether these findings, often based on receptor studies, have any significant clinical relevance. Futhermore, a comparison between Marvelon and a triphasic formula like Trigynon would be more appropriate since the triphasic formula can be considered as a breakthrough in the search for the best oral contraceptive.

Finally, many reports in the literature are uncritical in the definition of the control group. The aim of the present, preliminary report is to evaluate very carefully in a limited number of healthy women physical, hormonal and biochemical findings during the normal menstrual cycle and then to compare these with the same findings during intake of either Trigynon or Marvelon.

MATERIALS AND METHODS

Women who visited the outpatient department asking for oral contraception were informed about the study design. If no contraindications

for the use of oral contraceptives were found and if the woman gave informed consent, she was selected for the study. During a control cycle during the early follicular and late luteal phases body-weight, blood pressure, total cholesterol, HDL-cholesterol, fasting triglycerides, serum testosterone and testosterone in saliva values were measured. Then at random each women received either Trigynon or Marvelon which was continued for at least 6 months. During the third week of pill intake (maximal effect of the pill) in the third and sixth cycle the above-mentioned measurements were repeated. A glucose tolerance test was also performed in each woman during the early follicular phase of the cycle and repeated during the third week of the sixth pill cycle. 50 g of glucose were given and at 0, 10, 20, 30, 60 and 90 minutes both glucose and insulin were measured. All blood and saliva samples were taken at 09.00 a.m. (fasting) and the glucose tolerance tests also started at 09.00 a.m. All hormonal and biochemical measurements were performed by specific, precise and accurate means[3,4]. Statistical evaluation of the data was performed with Student's *t* test for the paired case comparing data from the early follicular phase of the cycle with those obtained in the same woman during the late luteal phase or during pill intake. Although it is our intention to study 30 women, 15 in each group, so far only 11 cases are ready for complete evaluation and their results will be presented.

Table 1 Body-weight (in kg) during the early follicular (EF) and late luteal (LL) phases of the menstrual cycle and during the third week of pill intake in the third and sixth pill cycle (3 OAC, 6 OAC). Control is the two subgroups together during the menstrual cycle

Regimen	*EF*	*LL*	*3 OAC*	*6 OAC*
Trigynon*	60.8±3.2	61.1±3.2	60.3±3.7	61.3±3.4
Marvelon*	62.0±1.1	62.4±1.3	61.6±1.3	61.2±1.4
Control**	61.4±5.8^{+}	61.7±5.8^{+}		

*Mean ±SE.
**Mean ±SD.
$^{+}$Values significantly different at $p = 0.005$.

RESULTS

Table 1 depicts body-weight during the control cycle and during the intake of either Trigynon or Marvelon. Body-weight increases significantly during the cycle. However, no influence on this para-

meter can be seen during pill intake compared with the early follicular phase. Table 2 shows systolic and diastolic blood pressure: no

Table 2 Blood pressure (in mmHg) during a control cycle and during intake of either Trigynon or Marvelon. Results are given as means ±SE

	Trigynon		*Marvelon*	
Phase of cycle	*Systolic*	*Diastolic*	*Systolic*	*Diastolic*
Early follicular	115 ±3.5	79.5±2.7	112 ±2.4	63 ±4.0
Late luteal	118 ±2.7	77.7±3.2	111.6±3.2	64 ±4.0
3 OAC*	114.6±6.0	72.4±4.1	112.0±2.3	63.2±3.4
6 OAC*	120 ±6.6	77.2±3.9	117 ±4.8	67.8±2.7

*Values determined during third week of pill intake in third (3 OAC) and sixth pill (6 OAC) cycle.

significant changes were observed during the normal cycle, nor during pill intake. Table 3 gives fasting triglyceride, total cholesterol, and HDL-cholesterol concentrations during the normal cycle and during pill intake. Fasting triglyceride values are significantly increased during the third Marvelon cycle. Both Trigynon and Marvelon tend to decrease total cholesterol value whereas no influence on

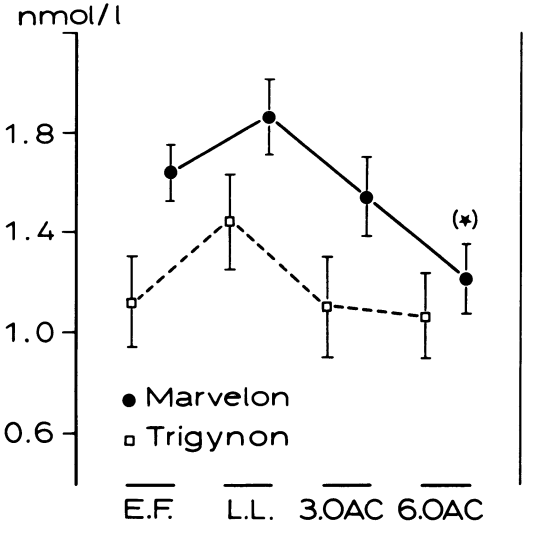

Figure 1 Serum testosterone levels (in nmoll^{-1}) in women using Trigynon or Marvelon during a control cycle and during pill intake. Values are shown as means ±SE. (*) Difference between values significant: $0.1 > p > 0.05$.
EF = Early follicular phase; LL = late luteal phase; 3 OAC = value during third week of third cycle; 6 OAC = value during third week of sixth cycle

Table 3 Fasting triglyceride, total cholesterol and HDL-cholesterol values during the control cycle and during intake of either Trigynon or Marvelon. Results are given as means ±SE. Control is the two subgroups together

Regimen	*I* *Early follicular*	*II* *Late luteal*	*III* *3 OAC**	*IV* *6 OAC**	*p value*		
					I–II	*I–III*	*I–IV*
Triglyceride ($mmol\,l^{-1}$)							
Trigynon	0.66±0.18	1.09±0.20	0.84±0.15	0.98±0.38	0.06	0.21	0.52
Marvelon	1.22±0.13	1.02±0.21	1.82±0.12	1.31±0.19	0.36	0.002	0.55
Control	0.92±0.14	1.33±0.12			0.32		
Total cholesterol ($mmol\,l^{-1}$)							
Trigynon	4.56±0.34	4.42±0.30	4.02±0.22	3.91±0.34	0.57	0.27	0.07
Marvelon	5.11±0.34	4.47±0.24	4.81±0.24	4.43±0.33	0.38	0.30	0.04
Control	4.81±0.24	4.44±0.22			0.26		
HDL-cholesterol ($mmol\,l^{-1}$)							
Trigynon	1.62±0.18	1.49±0.18	1.53±0.14	1.48±0.15	0.05	0.04	0.15
Marvelon	1.09±0.11	1.14±0.12	1.17±0.06	1.21±0.05	0.30	0.46	0.28
Control	1.38±0.13	1.33±0.12			0.31		

* Values determined during third week of pill intake in third (3 OAC) and sixth pill (6 OAC) cycle.

HDL-cholesterol is seen. No cyclic changes in these parameters are found.

Figure 1 shows the serum testosterone values. In both groups there is a tendency to higher testosterone levels during the late luteal phase. If the control cycles of the two groups are combined this difference is highly significant ($p = 0.003$). During the sixth month of Marvelon serum testosterone level is somewhat lower than during the early follicular phase ($p = 0.08$). All testosterone levels during pill intake are within the normal cyclic range and in general lower than during the late luteal phase of the cycle.

Testosterone in saliva gives much the same picture as testosterone in serum does: lower levels are obtained during pill intake in both

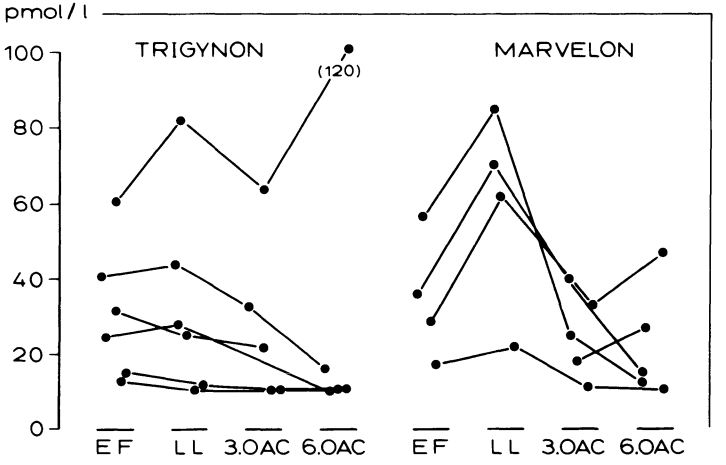

Figure 2 Saliva testosterone levels (in pmol l^{-1}) in women using Trigynon or Marvelon during a control cycle and during pill intake. Individual values are given.
EF = Early follicular phase; LL = late luteal phase; 3 OAC = value during third week of third cycle; 6 OAC = value during third week of sixth cycle

the Marvelon and the Trigynon groups (Figure 2). Since in both groups some values are missing, no statistical evaluation has been carried out between cyclic and pill results. If the data from all the control cycles until so far are combined ($n = 15$) then a highly significant increase ($p = 0.003$) is seen in the late luteal as compared with the early follicular phase of the cycle.

Figures 3 and 4 depict the serum glucose and insulin responses to 50 g glucose orally. In the Trigynon group there was a small ($p = 0.06$) increase in fasting glucose levels. In the Marvelon group this is less

obvious, whereas the glucose response as calculated as the area under the curve in this group increases significantly ($p = 0.04$). Also, fasting insulin levels ($p = 0.001$) and the insulin responses to glucose ($p = 0.005$) deteriorate during Marvelon use. However, the observed changes are still well within the normal range for healthy women.

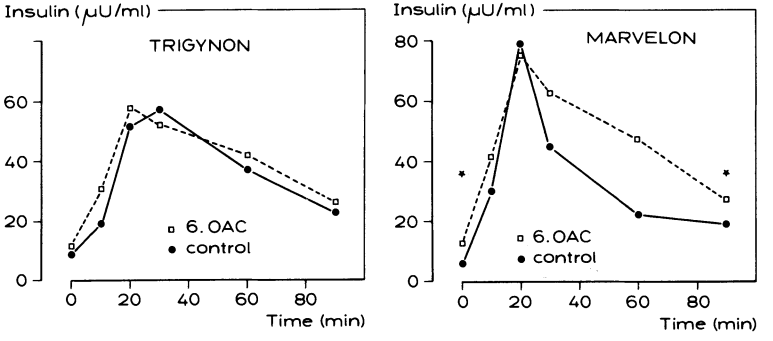

Figure 3 Blood glucose levels (mean ±SE) after 50 g glucose load (by mouth) during early follicular phase of control cycle and during treatment with Trigynon or Marvelon (third week of the six cycle 6 OAC). Difference between control and experimental valuessignificant: (*)$0.1 > p > 0.05$; *$p < 0.05$

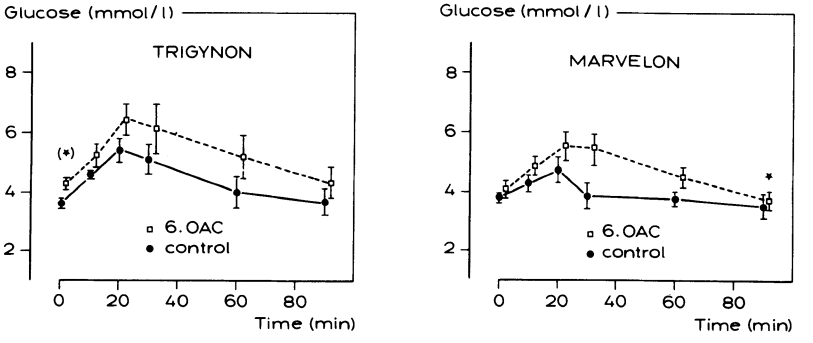

Figure 4 Mean serum insulin levels after 50 g glucose load (by mouth) during a control cycle and during intake of Trigynon or Marvelon (in third week of sixth cycle). * Difference between control and experimental values significant at $p < 0.05$. For further details, see the text

DISCUSSION

This study has so far demonstrated that all studies dealing with physical, biochemical and hormonal effects of oral contraceptives should have a well-defined group of normal, cyclic women as control.

Both body-weight and testosterone change during the cycle and if the late luteal phase is taken as reference point, most pill types will show a decrease both in serum testosterone and in testosterone in saliva.

Both total cholesterol and HDL-cholesterol do not change significantly during the normal cycle or during Trigynon – or Marvelon administration. Although no changes in HDL-cholesterol are seen during the cycle, this parameter does show significant changes in women used to physical exercise as compared with values in controls. This fact must also be taken into account when studies dealing with effects brought about by the intake of oral contraceptives are evaluated. The observed increase in fasting triglycerides during the third month of Marvelon use should be regarded with caution. Especially this parameter shows an intraindividual variation of 30% and the observed difference may very well be accidental[5].

Serum testosterone (total testosterone) and saliva testosterone (more a measure for free testosterone) values do not change during Trigynon or Marvelon intake if compared with the early follicular phase of the normal cycle, whereas the values are decreased if compared with the late luteal phase. Therefore, little or no differences are present between the examined pill types concerning influence on androgen metabolism.

Trigynon has little or no influence on glucose metabolism, whereas both glucose and insulin responses deteriorate significantly during Marvelon use. This has also been observed by others[6]. Although the change in the glucose response in general is thought to be brought about by oestrogens, the change in the insulin response is more complex and is also to be seen as an effect brought about by progestogens.

In conclusion, therefore, it cannot be decided solely from this study or studies measuring the same parameters which of these two pill types should be preferentially prescribed since all induced changes are well within the normal range. The triphasic pill, however, gives a significantly better cycle control as compared with combination pills like Marvelon (see Chapter 7) and this fact in general favours the use of this oral contraceptive.

Acknowledgements

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7
Clinical comparison between a monophasic preparation and a triphasic preparation

U. LACHNIT-FIXSON, S. AYDINLIK and J. LEHNERT

ABSTRACT

The triphasic preparation containing 6 coated tablets of 0.05 mg levonorgestrel (LN) + 0.03 mg ethinyloestradiol (EE), 5 coated tablets of 0.075 mg LN + 0.04 mg EE and 10 coated tablets of 0.125 mg LN + 0.03 mg EE (Triquilar®/Logynon®) was compared in a randomized multicentre trial with a monophasic combined pill composed of 0.15 mg desogestrel + 0.03 mg ethinyloestradiol (Marvelon®).

The main purpose of this study – planned for 6 treatment cycles – was to elucidate possible differences in cycle stability, i.e. the incidence of spotting and breakthrough bleeding episodes and failure of withdrawal bleeding to occur. A total of 555 women were enrolled and completed 3060 cycles. In a randomized fashion 278 of the volunteers were assigned to the triphasic preparation (preparation 1), and 277 to the monophasic combination (preparation 2). 84.5% of the women completed the six months treatment period on both preparations. However, whereas only 6.1% of triphasic takers discontinued medication prematurely because of medical reasons (side-effects), 11.9% of the women on the monophasic preparations did so, mainly because of bleeding irregularities. Calculated in terms of the total number of triphasic cycles the spotting rate was 6.4%, the BTB rate 1.2%. In 0.4% of all cycles spotting + BTB were recorded in the

same cycle. The corresponding figures for the monophasic preparation are as follows: spotting 16.5%, BTB 2.8% and spotting + BTB for the same cycles 1.1%. The amenorrhoea rate was 0.2% for the triphasic and 0.9% for the monophasic preparation.

All differences were statistically highly significant (Chi-square test) and not only confined to the beginning of medication, but also present in the 6th treatment cycle. Spotting rates in cycles 1 + 2 for preparation 1 = 10.9%, for preparation 2 = 28.5%; in cycle 6 for preparation 1 = 2.6%, for preparation 2 = 10.3%. BTB rates in cycles 1 + 2 for 1 = 2.0%, for 2 = 6.7%; in cycle 6 for 1 = 0.4%, for 2 = 2.2%.

Another interesting difference between the two preparations concerned body-weight, which remained constant in 75.2% of the triphasic users, but in only 61.1% of the monophasic users. Minor weight gains (+<2 kg) occurred in 11.3% of women taking preparation 1 and in 15.4% of women on preparation 2. Only 5.2% of the triphasic users versus 16.7% of the women on the monophasic combination had gained more than 2 kg after 6 months. These differences were also statistically highly significant.

Conclusion

Though it has been claimed that desogestrel has a higher progestogenic activity than levonorgestrel the triphasic levonorgestrel-contraceptive – which contains 40% less progestogen (1.925 mg) than the monophasic desogestrel-combination (3.15 mg) – provides a much better cycle control. Increase in body-weight occurs significantly more often in users of the desogestrel combination.

INTRODUCTION

There can no longer be any doubt that oral contraceptives containing low amounts of oestrogen *and* progestogen have less influence on parameters of the haemostatic system and metabolic functions than do high-dose preparations[1–3]. Therefore, their use is to be recommended, as WHO already have in 1978[4].

However, it is well known that a high rate of spotting and breakthrough bleeding may limit the acceptability of low-dose contraception. The triphasic approach seems to avoid this dilemma. It has been clearly demonstrated in two carefully conducted controlled

trials that the triphasic preparation Logynon provides significantly better cycle stability than Microgynon 30 though this monophasic preparation contains 40% more levonorgestrel than the triphasic product[5,6].

In 1981 Marvelon, a monophasic preparation containing 150 μg of the new progestogen desogestrel and 30 μg ethinyloestradiol was introduced in several European countries. Desogestrel has been claimed[7] to have higher progestational activity and fewer androgenic residual effects than levonorgestrel.

The aim of the present study was to assess the overall tolerance, principally in terms of cycle control, of this new monophasic preparation in comparison with the triphasic levonorgestrel-containing pill (Table 1).

Table 1 Composition of trial preparations

Marvelon	*Triquilar (Logynon)*
0.150 mg desogestrel 0.03 mg ethinyloestradiol	6 coated tablets: 0.05 mg levonorgestrel 0.03 mg ethinyloestradiol
	5 coated tablets: 0.075 mg levonorgestrel 0.04 mg ethinyloestradiol
	10 coated tablets: 0.125 mg levonorgestrel 0.03 mg ethinyloestradiol

In order to establish statistically significant differences between the two preparations the planning design for the study required the inclusion of a minimum of 200–250 women per trial group for a period of six cycles.

MATERIALS AND METHODS

The multicentre comparative trial between the two preparations was conducted in Austria, Germany, the Netherlands and the UK. Both clinics and gynaecologists in private practice participated in the trial. A total of 555 women were enrolled and followed up for six treatment cycles. The participants were allocated to the two treatment groups in a randomized fashion, 278 to the triphasic and 277 to the monophasic

preparation. More than 60% of the women were below the age of 30 in both groups. Also, there was no difference with regard to parity, number of miscarriages or intermenstrual bleeding.

Identical protocols suitable for computer analysis were used. After careful instruction about the purpose of the study each woman was asked to note details concerning cycle length, duration and intensity of withdrawal bleeding, abnormal bleeding episodes and other items on a special chart. A routine examination including blood pressure and body-weight and a detailed gynaecological check-up was done at admission. Follow-up visits were done after one, three and six cycles. Then body-weight and blood pressure were checked and the data from the individual bleeding charts transferred to the computer protocols. Spontaneously mentioned or obvious side-effects were also recorded.

RESULTS

The 555 women completed a total number of 3060 cycles, 1536 cycles on Logynon and 1524 cycles on Marvelon.

The number of women completing each cycle (n = 278 for Logynon

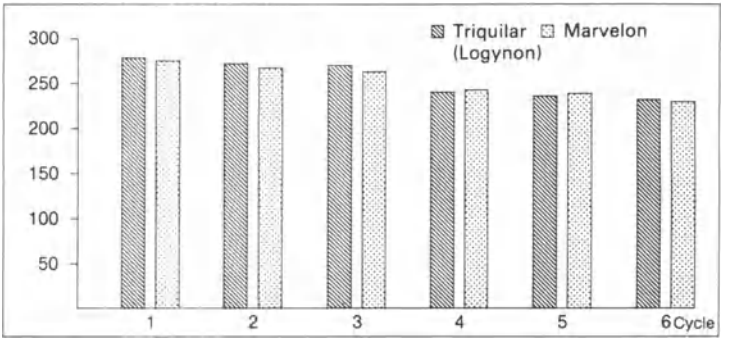

Figure 1 Number of women completing treatment cycles in both experimental groups

and n = 277 for Marvelon) is shown in Figure 1. 84.5% of the women finished the 6-month treatment period on the two preparations. However, whereas only 6.1% of triphasic takers discontinued medication prematurely for medical reasons, 11.9% of the women on the

monophasic combination did so, mainly because of bleeding irregularities and headaches.

Efficacy

Omission of tablets was admitted in 23 Logynon and in 19 Marvelon cycles. One pregnancy occurred in the triphasic group, none in the monophasic group. This one pregnancy was classified by the attending physician as clearly due to patient failure: a young girl of 15 years had omitted two consecutive tablets during the first days of the third cycle.

Cycle control

Both formulations exerted a normalizing effect on cycle length and duration of bleeding, especially in women with previously prolonged bleeding episodes.

Equally, the two preparations reduced previously heavy bleedings to the same extent. However, 'scanty' bleeding was reported more frequently by women on the monophasic combination than by

Table 2 Percentage of patients with intensity of menstrual flow before and during treatment

Intensity	*Before treatment*	*6th Logynon cycle*	*6th Marvelon cycle*
Scanty	7.3	18.3	32.3
Normal	82.9	79.6	65.5
Heavy	9.8	2.1	2.2

women using the triphasic formulation, as can be seen in Table 2. Failure of withdrawal bleeding to occur was comparatively rare in both groups. The rate was 0.2% for the triphasic and 0.9% for the monophasic preparation; the difference was statistically significant ($p < 0.01$).

Of special interest were possible differences in the incidence of spotting and breakthrough bleeding: calculated in terms of the total number of triphasic cycles the spotting rate was 6.4%, the BTB rate 1.2%. In 0.4% of all cycles spotting and BTB were recorded in the same cycle. The corresponding figures for the monophasic preparation are much higher: spotting 16.5%, BTB 2.8% and both episodes in the

same cycle 1.1%. Applying the Chi-square test these differences are highly significant ($p < 0.001$).

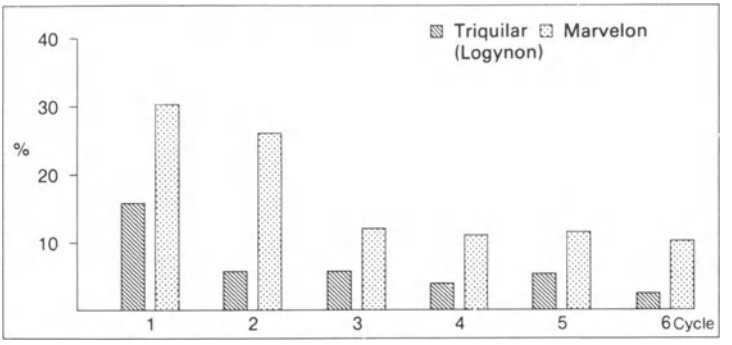

Figure 2 Percentage of spotting episodes in women completing treatment cycles in both experimental groups

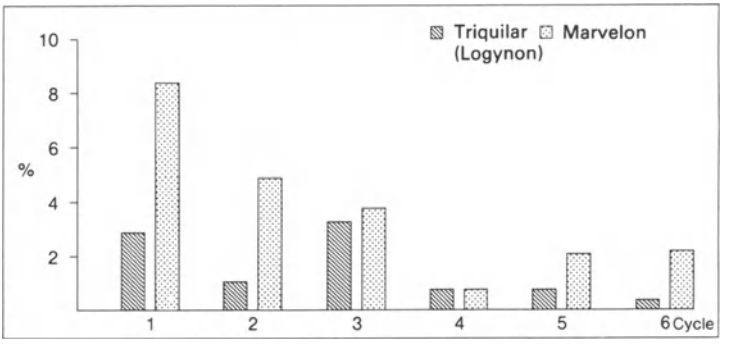

Figure 3 Percentage of breakthrough bleeding episodes in women completing treatment cycles in both experimental groups

Even more informative are Figures 2 and 3 which clearly demonstrate that – though most evident in the first two cycles – differences persisted during the whole treatment period.

Body-weight and blood pressure

Another interesting difference between the two preparations concerned body-weight, which remained constant in 75.2% of the tri-

phasic users, but in only 61.1% of the monophasic users. Minor weight gains (+ < 2 kg) occurred in 11.3% of women on Logynon and in 15.4% of women on Marvelon. Only 5.2% of the triphasic users, as against 16.7% of the women on the monophasic combination, had

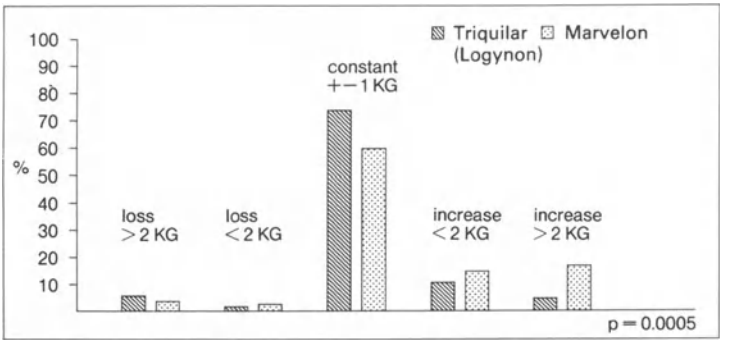

Figure 4 Percentage of experimental groups showing changes in body-weight after 6 months' treatment. * Difference between groups significant at $p = 0.0005$

gained more than 2 kg after 6 months (Figure 4). These differences are also statistically highly significant. Minor and major weight losses were similar with both preparations.

Blood pressure remained constant in the vast majority of women on both products. After 6 months Logynon a fall was recorded in four of five cases with RR values over 140/90 mmHg at start of therapy, while of 219 women with normal blood pressure, increases to values over 140/90 mmHg were recorded in four. With Marvelon normalization took place in two out of three women with RR values over 140/90 mmHg. From 222 women with normal blood pressure seven developed values over 140/90 mmHg within 6 months (Table 3).

Side-effects

Both low-dose products were well tolerated. Only few women reported the subjective side-effects commonly associated with oral contraceptive use under the two preparations. Headaches, including the migrainous type, and complaints about breast tenderness were somewhat more frequent in the Marvelon group (Table 4).

Acne developed in four women on Marvelon, but in only one woman on Logynon.

DISCUSSION

The triphasic levonorgestrel contraceptive provides a much better cycle control than the monophasic desogestrel combination. The differences in intracyclical bleeding episodes between the triphasic levonorgestrel preparation and the monophasic 150μg desogestrel combination are even more pronounced than those observed in other comparative studies between the triphasic product and a monophasic 150μg levonorgestrel combination[5,6].

Table 3 Blood pressure changes in four subjects using Logynon and in seven subjects using Marvelon

Triphasic (Logynon)		*Monophasic (Marvelon)*	
Last cycle before medication	*6th cycle*	*Last cycle before medication*	*6th cycle*
1. 125/85	135/110	1. 125/70	150/95
2. 140/90	145/90	2. 130/90	145/80
3. 140/80	160/70	3. 120/70	145/75
4. 110/60	150/80	4. 130/70	145/90
		5. 130/70	140/100
		6. 140/85	150/90
		7. 140/90	160/100

Table 4 Percentage of women suffering subjective side-effects

Side-effect	*Triphasic group*	*Monophasic group*
Nausea	4.3	4.0
Headache	4.6	5.4
Migraine	0.7	1.4
Breast tenderness	2.2	5.4

Since it has been claimed that desogestrel has higher progestogenic activity[7], this is a rather unexpected finding. The results of our comparative clinical study once more clarify that in oral contraception one normally deals with combined oestrogen–progestogen effects.

An optimal oestrogen–progestogen ratio, for instance, may be more important for the overall effect of the preparation than partial qualities of the hormonal components.

Also, androgenic residual effects of progestogens are clinically almost irrelevant in modern low-dose preparations. Weight gain and skin problems like acne and seborrhoea are said to be clinical signs of androgenic activity of oral contraceptives. There is no evidence for a higher incidence of weight gain and acne with the triphasic levonorgestrel preparation in comparison with the desogestrel combination. On the contrary, increase in body-weight occurred significantly more often in users of the desogestrel combination. Likewise acne – though very rare with both products – occurred in four cases as opposed to only one with the triphasic preparation.

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8
Comparative study of lipid metabolism and endocrine function in women receiving levonorgestrel- and desogestrel-containing oral contraceptives

U. J. GASPARD, M. A. ROMUS and D. GILLAIN

SUMMARY

The aim of this randomized study was to evaluate potential alterations of the lipid profile and endocrine function in carefully matched healthy female volunteers investigated before and at 6 months' use of three new oral contraceptives (OCs): Logynon (n=13), a triphasic OC containing low doses of ethinyloestradiol (EE) + levonorgestrel (LNg), Marvelon (n=14), a monophasic OC containing low doses of EE + desogestrel (DOG, a new progestogen derived from LNg) and Ovidol (n=11), a sequential OC containing higher doses (50 μg) of EE + DOG.

At the 6th month of OC use, results were as follows: *(1) Lipid profile:* Total-C, HDL-C, LDL-C and their ratios were unchanged; Apo AI/Apo B ratio was somewhat increased with all three OCs. VLDL + total triglycerides were significantly increased with Ovidol only. *(2) Hormones:* PRL levels were unchanged. FSH, LH, E2 and P were low, indicating effective ovulation inhibition in all individuals. Free T levels were equally well inhibited by all three OCs due to

increased SHBG (Ovidol + 397% from basal, Marvelon + 352%, Logynon + 127%). PRA was significantly increased with Ovidol only. Free F was unchanged.

In conclusion, Marvelon, and particularly Ovidol (marked increase in VLDL, TG, SHBG, CBG, PRA) are distinctly more oestrogenic than Logynon.

INTRODUCTION

Laboratory findings indicate that the amount and chemical nature of oestrogens and progestogens contained in oral contraceptives (OCs) are correlated with alterations in blood coagulation factors, glucose and lipid metabolism, probably resulting in clinical problems for the OC users[1].

Progestogens contained in the OCs are derived mainly from 19-nortestosterone and may exert metabolic actions depending not only on their progestagenic but also on their androgenic and anti-oestrogenic properties. In this study, we compared the influence on serum lipids and on various hormonal parameters of a triphasic OC containing particularly low doses of a well-known 19-nortestosterone-derived progestogen, levonorgestrel (LNg) with a sequential and a monophasic preparation containing low doses of desogestrel (DOG), a new 3-deoxo-11-methylene derivative of LNg. We tried to assess whether the metabolic and hormonal alterations observed indicated any difference of action between DOG and LNg.

SUBJECTS AND METHODS

Subjects

All women studied (n=37) were healthy, young medical students (mean age 22.75 years, mean ideal body-weight 101%), who had never used oral contraception previously or had stopped OCs for at least 8 weeks prior to the study.

In each individual, a fasting blood sample was obtained at 08.30 a.m. 7 days before menstruation during a spontaneous cycle (control cycle). After exclusion of any contraindication to OC use and following a normal gynaecological examination, three groups of, respectively 13, 10 and 14 women were constituted at random. All subjects from group I received Trigynon for six cycles, beginning on day 1 of

the first treatment cycle, with a 7-day free interval between each treatment cycle. The subjects from group II were assigned Ovidol in a similar way and women from group III received Marvelon. A second blood sample was obtained the last 3 days of the sixth cycle of OC use in each individual. Composition of the OCs is given in Table 1.

Table 1 Oral contraceptives used

Nature of the preparation	*Triphasic*	*Sequential*	*Monophasic*
Trade names	Trigynon	Ovidol	Marvelon
Components	1. EE 0.03 mg + LNg 0.05 mg (days 1–6) 2. EE 0.04 mg + LNg 0.075 mg (days 7–11) 3. EE 0.03 mg + LNg 0.125 mg (days 12–21)	1. EE 0.05 mg (days 1–7) 2. EE 0.05 mg + DOG 0.125 mg (days 8–21)	EE 0.03 mg + DOG 0.150 mg (days 1–21)

EE = Ethinyloestradiol; LNg = Levonorgestrel; DOG = Desogestrel.

Methods

FSH, LH, PRL, progesterone (P), oestradiol (E_2), total testosterone (T), total cortisol (F), aldosterone (Aldo) and plasma renin activity (PRA), were measured by radioimmunoassay, and estimations of sex hormone binding globulin (SHBG), transcortin (CBG), free T and free F were made according to procedures previously described[2]. Serum lipids and lipoproteins were determined by enzymatic, chemical and electroimmunoassay methods reported elsewhere[3].

RESULTS

Lipids

Changes in serum lipid and lipoprotein concentrations after 6 months of use of each OC are detailed in Table 2.

Starting values of lipid concentrations were similar in the three groups of patients before treatment. After 6 months of OC use, total TG were significantly more elevated in the Ovidol group, apoprotein

B levels were significantly reduced in the Marvelon group and accordingly Apo AI/Apo B ratio was increased.

Hormones

Alterations of hormone levels after 6 months of OC use are given in Table 3. All hormone and carrier protein levels were similar in the three groups before treatment. After 6 months of OC use FSH and LH levels were significantly more inhibited in the Marvelon group; SHBG levels were significantly more elevated in the Ovidol and Marvelon groups; and CBG levels were more elevated in the Ovidol group.

Table 2 Serum lipid profile at 6 months of oral contraceptive use

	Group mean values (pretreatment = 100%)		
Variable	*Triphasic, Trigynon (EE+LNg)*	*Monophasic, Marvelon (EE+DOG)*	*Sequential, Ovidol (EE+DOG)*
Total triglycerides	+ 29 (%)	+ 21	+ 90**
Total phospholipids	+ 8.8	+ 7.2	+ 16.3**
Total cholesterol	+ 4.6	+ 1.8	+ 9.6
HDL cholesterol	0	+ 5.3	+ 1.7
LDL cholesterol	+ 1	− 4	+ 4
HDL cholesterol: total cholesterol	− 2	+ 3.8	− 6
LDL cholesterol: HDL cholesterol	+ 4	− 7.7	− 1.1
Apoprotein A_I	+ 13.2*	+ 14.5*	+ 18.5*
Apoprotein B	+ 2.2	− 19*	+ 11.7
Apo A_I:Apo B	+ 18.4	+ 40.9**	+ 22

*$p < 0.05$; **$p < 0.001$ (paired t test for comparison of pretreatment and 6-month values).
EE = Ethinyloestradiol; LNg = Levonorgestrel; DOG = Desogestrel.

DISCUSSION AND CONCLUSIONS

Lipids

This study clearly shows, as indicated already by Larsson-Cohn *et al.*[4], that the triphasic formulation provides a favourable EE:LNg ratio which allows the androgenic–antioestrogenic properties of LNg to be appropriately balanced by the oestrogen content for effects on

Table 3 Influence of oral contraceptives on plasma hormone levels before and after 6 months of use. Results are given as means ±SE*

Plasma hormones	*Trigynon* (n = 13)		*Ovidol* (n = 10)		*Marvelon* (n = 14)	
	Pretreatment	*6th month*	*Pretreatment*	*6th month*	*Pretreatment*	*6th month*
FSH ($mIU\,ml^{-1}$)	4.23±0.67	2.65±0.57 *NS*	4.14±0.62	2.84±0.67 *NS*	3.60±0.48	1.97±0.35 *0.001*
LH ($mIU\,ml^{-1}$)	6.61±0.93	4.81±1.08 *NS*	9.30±3.66	5.30±1.32 *NS*	6.84±1.35	3.09±0.45 *0.01*
PRL ($\mu U\,ml^{-1}$)	463±111	428±71 *NS*	430±68	442±63 *NS*	482±99	320±81 *NS*
E2 ($pg\,ml^{-1}$)	152±29	34±5 *0.006*	124±27	33±7 *0.02*	163±24	57±30 *0.02*
P ($ng\,ml^{-1}$)	8.10±1.64	0.31±0.26 *0.01*	6.61±1.40	0.17±0.02 *0.006*	9.59±2.33	0.20±0.04 *0.001*
Total T ($pg\,ml^{-1}$)	486±34	324±50 *0.02*	507±64	393±49 *NS*	429±66	312±46 *0.07*
Free T ($pg\,ml^{-1}$)	5.08±1.06	1.90±0.31 *0.002*	5.99±1.36	1.60±0.22 *0.002*	4.90±1.47	1.50±0.20 *0.005*
SHBG ($nmol\,l^{-1}$)	84±14	191±25 *0.000*	70±7	348±37 *0.000*	59±8	267±22 *0.000*
Total F ($ng\,ml^{-1}$)	193±10	405±34 *0.000*	173±12	460±37 *0.000*	176±11	393±24 *0.000*
Free F ($ng\,ml^{-1}$)	11.7±1.0	13.1±1.7 *NS*	10.5±1.1	15.7±1.8 *NS*	10.6±1.2	14.2±2.4 *NS*
CBG ($mg\,l^{-1}$)	43.4±2.6	80.1±2.0 *0.000*	40.8±1.7	94.5±4.5 *0.000*	40.8±2.6	83.7±2.6 *0.000*
Aldo ($pg\,ml^{-1}$)	248±31	241±59 *NS*	220±28	274±29 *NS*	240±40	304±43 *NS*
PRA ($ng\,ml^{-1}\,h^{-1}$)	2.10±0.30	4.38±1.07 *NS*	2.06±0.29	6.15±1.58 *0.01*	3.05±1.58	3.51±0.77 *NS*

*Paired Student's t test used for comparison of pretreatment and 6th month values and result given in italics; *NS* = not significant.

metabolic end-points such as HDL-C, apolipoprotein A_I concentrations, etc. The triphasic preparation containing LNg and the two other preparations containing DOG had no influence on total-C, HDL-C or LDL-C. HDL-C/total-C and LDL-C/HDL-C ratios were unchanged while Apo A_I/Apo B ratio was slightly increased (mainly during Marvelon treatment). These observations are corroborated by other studies[5,6] and confirm an apparent lack of atherogenic effect of these preparations on the lipid profile. However, marked oestrogenic dominance of Ovidol is abided by a very important increase in VLDL and TG, not found with the other preparations tested.

Hormones and carrier proteins[2]

All three OCs inhibited pituitary gonadotrophin secretion and gonadal function in all the cases studied. All three OCs exerted dominant oestrogenic effects as exemplified by marked and significant increases in CBG (Ovidol >> Marvelon > Trigynon). Free F levels are, however, unchanged.

The lower antioestrogenic activity of DOG *vs.* LNg is best exemplified in our study by a significantly greater rise in SHBG during Marvelon and Ovidol treatment (Ovidol > Marvelon >> Trigynon). However, free T levels are equally effectively suppressed by all three preparations.

In summary, oestrogen dominance is slightest in Trigynon but sufficient to balance the antioestrogenic properties of LNg and the triphasic preparation seems well equilibrated. Marvelon and especially Ovidol are more oestrogenic (less antioestrogenic) preparations. The administration of the latter one is accompanied by an excessive increase in VLDL, TG, SHBG, CBG and PRA.

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9
Androgenic properties of progestogens used in oral contraceptives

J. SPONA

SUMMARY

Recent reports claimed 3-keto-desogestrel to exert less androgen-related side-effects than levonorgestrel. These claims were based on data obtained from receptor assays performed as single determinations. We were prompted to investigate androgenic actions since our own clinical experience with these two progestins did not suggest differences in androgen-related side-effects. In addition, actions of cyproterone acetate (CPA) were studied. Relative binding affinities for the androgen receptor were investigated in cytosol samples of mice kidneys. β-glucuronidase activities were determined in kidneys of adult mice treated subcutaneously with 0.05, 0.5 and 1.5 mg of progestational agents for 7 days.

RBA for the androgen receptor of DOG, LNg and CPA were 0.316 $\pm$ 0.092, 0.195 $\pm$ 0.053 and 0.204 $\pm$ 0.022, respectively, as registered in seven different experiments. Statistical analysis of data revealed significantly greater RBA for DOG than for LNg ($p < 0.02$). No differences in β-glucuronidase activities between DOG and LNg were noted for 0.05 and 0.5 mg doses whereas a significantly greater enzyme stimulation by DOG was registered for the 1.5 mg dose ($p < 0.005$).

CPA was found to exert synandrogenic action on β-glucuronidase activities at the lower dose level and antiandrogenic action at the

higher dose levels. The present data suggest that 3-keto-desogestrel exerts more pronounced androgenic actions on target tissues than levonorgestrel. Clinical data indicate no greater differences in androgen-related side-effects between oral contraceptives with 3-keto-desogestrel or levonorgestrel.

INTRODUCTION

Progestagens may structurally be derived from pregnane, androstane or oestrane. Concomitant androgenic or oestrogenic activities arise from these structural relationships. Androgenic and oestrogenic potencies of progestational components of oral contraceptives are well documented by pharmacological studies in animals and men[1,2]. Levonorgestrel, which is among the most commonly used progestogens in oral contraceptives, is essentially without oestrogenic effects but exerts androgenic action. Concomitant androgenic potency of levonorgestrel was recorded to be greater than that of norethisterone[3]. Androgen-related side-effects are unwanted and should be kept as small as possible. Efforts to develop new progestins resulted in the synthesis of desogestrel and its biologically active metabolite 3-keto-desogestrel (13-ethinyl-11-methylene-18, 19-dinor-17α-pregn-4-en-20-yn-17-ol-3-one)[4]. Desogestrel and 3-keto-desogestrel, respectively, was reported to lack androgenicity in the dose used for oral contraception[5].

The aim of the present investigation was to study relative binding affinities (RBA) for the androgen receptor in mouse kidney cytosol of different progestins. In addition, steroid–receptor interactions were correlated with effects on the activity of mouse kidney β-glucuronidase. This model system was reported to allow to estimate androgenic, antiandrogenic and synandrogenic actions of progestins[6]. We were prompted to report on the results of the present experiments since 3-keto-desogestrel was described to exert less androgenicity than other progestins used in oral contraceptives. This reduced androgen action of 3-keto-desogestrel was derived from receptor studies[7].

MATERIALS AND METHODS

Mouse kidney cytosol was used as a model system to test for relative binding affinities of various progestins. Adult female mice of HIM/OF1 (Swiss) strain (Institute for Animal Breeding, School of Medicine,

University of Vienna) were used throughout this study. Animals were housed in a temperature-controlled room lit for 12 h per day and had unrestricted access to food and water. Mice were used between 1 and 2 weeks after shipment. Mouse kidney cytosol samples were used to estimate relative binding affinities (RBA) of 3-keto-desogestrel, levonorgestrel, progesterone, dihydrotestosterone, 17α-propylmesterolone and cyproterone acetate. All steroids were obtained from Schering AG, W. Germany. Animals were killed by decapitation, and the kidneys were excised and placed in chilled saline. All procedures were carried out at 0–4 °C. Determination of RBA was carried out by modification of methods described previously[8]. Briefly, cytosol was obtained by homogenizing six kidneys in 2.5 ml of TEGD-buffer (10 mmol l^{-1} Tris, 1 mmol l^{-1} EDTA, 30% glycerine, 6 mmol l^{-1} dithiothreitol, pH 7.2) in a glass–Teflon Potter–Elvehjem-type homogenizer. The homogenate was filtered through a stainless steel grid (160 mesh) and the filtrate was centrifuged at 800 g for 10 min. The supernatant was centrifuged at 105 000 g on a Spinco L2-65B (Beckman Instrumenta, Palo Alto, Ca., USA) for 60 min to obtain the cytosol fraction. Cytosol samples (100 μl) were incubated with 120 000 cpm (100 μl) of [^{3}H]-R1881 (specific activity 81 Ci mmol^{-1}, New England Nuclear, Boston, Ma., USA) in the presence of 0–10 000 nmol l^{-1} of compound to be tested. Incubation was done at 0–4 °C for 2 h and 500 μl of DCC suspension (0.6% Norit A, 0.06% Dextran T-70 in TEGD-buffer) was added. Incubation was continued for another 20 min and tubes were centrifuged at 3000 g for 15 min. The supernatant was transferred to counting vials, 10 ml Optifluor (Packard Instruments, Downers Grove, Ill., USA) was added and radioactivity was counted in a scintillation counter Packard model 460 CD.

Processing of data was performed by a computer program developed in our laboratory (unpublished) and run on a PDP 11/34 DEC Datasystem (Digital Equipment Corporation, Maynard, Mass., USA). Unlabelled R1881 was used as reference substance to determine RBA, which was calculated by dividing the concentration of R1881 at the 50% intercept by the 50% intercept concentration of the steroid to be tested.

Incubations were carried out in triplicate and RBA data were derived from seven different experiments. Statistical evaluation of data was performed by Student's t test.

Stimulation of β-glucuronidase activity was used as a parameter to

test for androgenicity of various steroids. Progestins were subcutaneously applied to adult female mice at 0.05, 0.5 and 1.5 mg daily dose through 7 days unless otherwise stated. In addition, testosterone was applied either alone or in combination with cyproterone acetate or 17α-propylmesterolone. Steroids were dissolved in sesame oil with 10% ethyl alcohol. Control groups were injected with vehicle only. Each treatment group consisted of five animals. The mice were killed 4 h after the last application. Kidneys were excised and stored in liquid nitrogen until assayed for β-glucuronidase activity, which was determined by methods published previously[9]. In brief, each kidney was homogenized in 2 ml of 0.1 mol l^{-1} acetate buffer, pH 4.5 in a glass–Teflon Potter–Elvehjem type homogenizer. The homogenate was diluted to 10 ml with buffer and two 0.1 ml aliquots were used for enzyme assay. Tubes containing 0.1 ml of the homogenates, 0.8 ml of 0.1 mol l^{-1} acetate buffer, pH 4.5, and 0.1 ml of 0.01 mol l^{-1} phenolphthalein glucuronic acid were incubated at 37 °C for 80 min. The reaction was stopped by heating in a boiling water bath. Then 1.5 ml of 0.22 mol l^{-1} glycine 0.22 mol l^{-1} NaCl were added and the mixture centrifuged at 3000 g for 10 min. The supernatant (2 ml) was mixed with 4 ml glycine solution and OD at 540 nm determined after another 10 min. Similarly, OD measurements were carried out with various phenolphthalein standard concentrations under standard assay conditions. Results were expressed as % enzyme activity of control groups. Data are means ±SD of enzyme activities in 10 kidneys of each group.

RESULTS

Data on the RBA of levonorgestrel, 3-keto-desogestrel, progesterone, cyproterone acetate, dihydrotestosterone and 17α-propylmesterolon are shown in Figure 1. Results are based on using R1881 as reference when calculating RBA values. Statistical analysis of RBA data reveals that 3-keto-desogestrel exhibits a greater affinity for the androgen receptor than levonorgestrel ($p < 0.02$). Progesterone shows only residual affinity for the androgen receptor in mouse kidney cytosol, and dihydrotestosterone has the greatest RBA of all steroids tested. RBA of cyproterone acetate is not different from that observed for levonorgestrel, and 17α-propylmesterolone has a RBA similar to that of cyproterone acetate.

Increasing doses of 3-keto-desogestrel resulted in linear increase

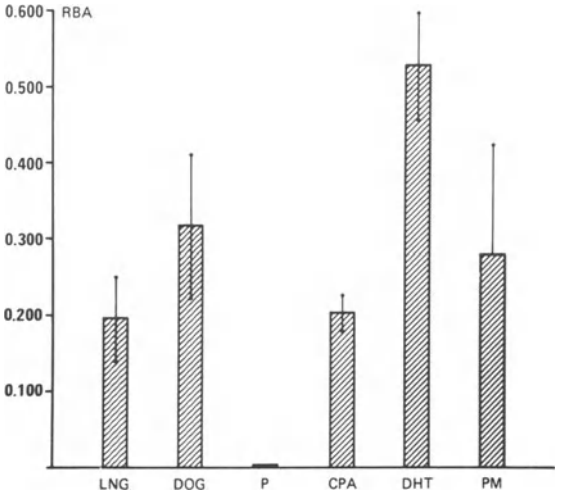

Figure 1 Relative binding affinities (RBA) of levonorgestrel (LNG), 3-keto-desogestrel (DOG), progesterone (P), cyproterone acetate (CPA), dihydrotestosterone (DHT) and 17α-propylmesterolone (PM) were determined by using mouse kidney cytosol and ^{3}H-labelled R1881 as reference ligand. Other details are given in Materials and Methods

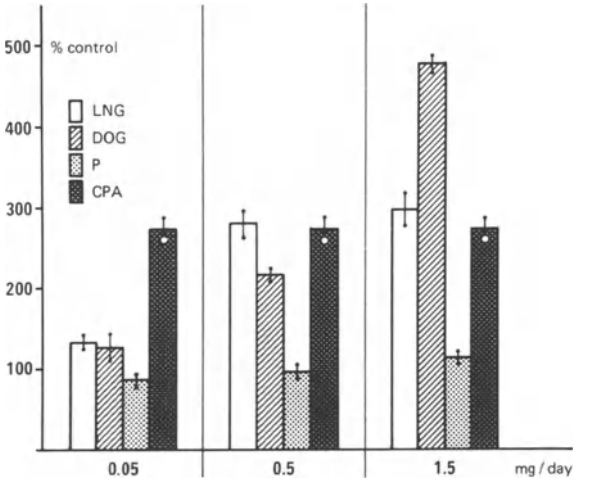

Figure 2 Determination of β-glucuronidase activity. Stimulation by levonorgestrel (LNG), 3-keto-desogestrel (DOG), progesterone (P) and cyproterone acetate (CPA) of the enzyme was carried out by subcutaneous application of 0.05, 0.5 and 1.5 mg of each compound through 7 days. Results are given as percentages of vehicle-treated control animals (100%). All other procedures are given in Materials and Methods

of β-glucuronidase activity, whereas enzyme activity levelled off at daily dose of 0.5 mg (Figure 2). No stimulation by progesterone of β-glucuronidase activity was observed at all doses applied. Statistical analysis revealed significantly greater β-glucuronidase activity at 1.5 mg dose of 3-keto-desogestrel than at the same levonorgestrel regimen ($p < 0.005$). But greater enzyme stimulation by levonorgestrel than by 3-keto-desogestrel was found at the 0.5 mg dose ($p < 0.05$). Progesterone, on the other hand, did not affect β-glucuronidase activity at the doses tested. Cyproterone acetate was registered to stimulate enzyme activity to 274±13% of controls at all doses tested, and no dose-dependent increase of β-glucuronidase activity was noted (Figure 2). On the other hand, testosterone greatly enhanced enzyme activity in a dose-dependent fashion up to the 0.5 mg dose. But β-glucuronidase activity was slightly lowered when the dose was

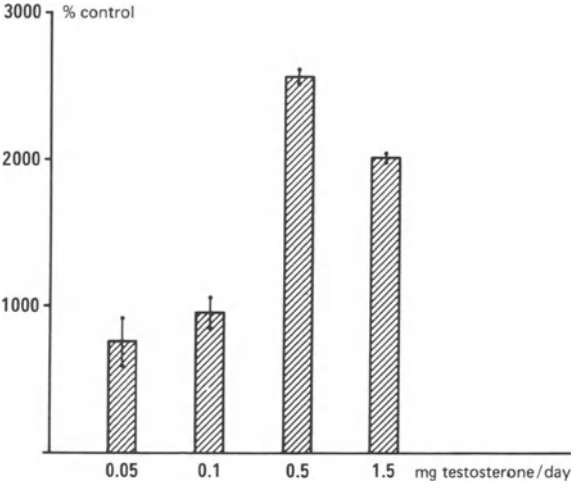

Figure 3 Stimulation by testosterone of β-glucuronidase activity. Data are given as percentages of controls (100%)

further increased (Figure 3). The application of a constant dose of 0.1 mg testosterone plus increasing doses of cyproterone acetate resulted in patterns of β-glucuronidase activity which indicated that cyproterone acetate possessed synandrogenic properties at the lower dose level and exhibited antiandrogenic actions at the higher doses (Figure 4). Similarly, 17α-propylmesterolone which was reported to possess strong antiandrogenic properties in an animal model system

(F. Neumann, personal communication) was noted to exhibit RBA similar to that of cyproterone acetate (Figure 1) but was found to be strongly synandrogenic in the dose range tested (Figure 5).

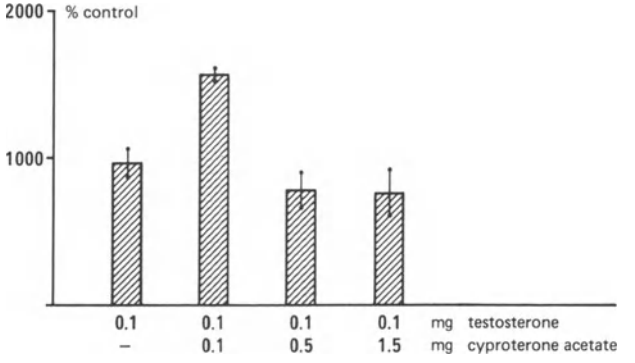

Figure 4 Determination of β-glucuronidase activity after stimulation by a combination of testosterone plus various doses of cyproterone acetate. Results are given as percentages of controls (100%)

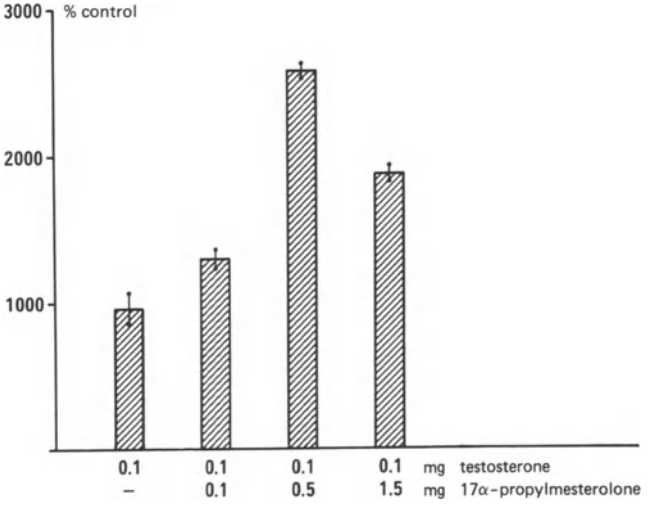

Figure 5 Influence of 17α-propylmesterolone on testosterone-stimulated β-glucuronidase activity. Data are given as percentages of controls (100%)

DISCUSSION

Androgenicity of progestogens is well documented, as is stimulation by progestins of the male reproductive tract[10] and of masculinization[11,12]. It was noted that compounds structurally related to 19-nortestosterone were in general more androgenic than those that were derived from progesterone[1]. This general observation may lead one to conclude that 3-keto-desogestrel and levonorgestrel should not differ much in their inherent androgenic potency. The only structural differences between levonorgestrel and 3-keto-desogestrel is the absence of an oxygen atom at C–3 and the presence of a methylene group at C–11 in 3-keto-desogestrel. These differences in structure were reported to result in binding of 3-keto-desogestrel to the androgen receptor at a markedly lower level than that of levonorgestrel and of other progestational agents[7]. Additionally, desogestrel was reported to display in pharmacological experiments progestational properties and an ovulation-inhibiting effect without any other actions worth mentioning[13].

The present experiments were aimed at delineating in more detailed studies some possible differences between the two compounds. Present evidence suggests that progestins that mimic or modify androgen actions compete with testosterone and dihydrotestosterone for binding sites at the cytoplasmic androgen receptor from kidney[14] and male reproductive tract[15,16]. The mechanism of progestogen interaction with the androgen receptor is postulated to be due to the androgen-binding protein being an allosteric protein with multiple binding sites which will accept both androgens and progestins[17].

The most interesting result of the present investigation is the observation that 3-keto-desogestrel exhibited significantly greater affinity for the mouse kidney cytosol receptor than levonorgestrel (Figure 1). Previously, it was reported on experiments with rat prostate cytosol that 3-keto-desogestrel and levonorgestrel exhibited similar affinities for the cytoplasmic androgen receptor[18]. Present and previous[18] results differ from earlier observations[7] in which markedly reduced interactions of 3-keto-desogestrel with the androgen receptor were reported as compared with the binding of levonorgestrel to the androgen-binding protein. Several explanations for these discrepancies are possible. One is that earlier observations[7] are results of only one single experiment whereas the present and previous[18] data are based on at least six different determinations.

Another most intriguing point of the present investigation is the finding that levonorgestrel and 3-keto-desogestrel do not differ much in their androgenic properties at the lower dose levels tested to study the effects on β-glucuronidase activity (Figure 2). But 3-keto-desogestrel was noted to stimulate β-glucuronidase activity to a significantly greater extent than levonorgestrel at higher doses. The present results are more indicative of the degree of androgenicity than conclusions drawn from receptor assays only[7]. Assay of β-glucuronidase activity was noted to be a valid indicator which allowed differentiation between androgenic, antiandrogenic and synandrogenic actions of progestogens[6].

Dissociation of RBA and biological activity was noted in experiments with cyproterone acetate (Figures 1, 2 and 4). These data add further evidence to the notion that cytosol receptor interaction may not be used to derive biological activity of a steroid. Similarly, no correlation between action of 17α-propylmesterolone on β-glucuronidase activity and RBA was registered. Therefore, conclusions on androgenicity of 3-keto-desogestrel as drawn from receptor data[7] are not valid. The present data and previous observations[19] indicate that receptor data cannot be used to predict biological activities accurately. Furthermore, present data corroborate clinical observations (Chapter 6) which suggest slightly greater androgen-related side-effects in oral contraceptives containing desogestrel than in those in which levonorgestrel is used.

Acknowledgements

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Effect of oral contraceptives upon serum lipoprotein pattern in healthy women

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INTRODUCTION

Epidemiological studies have clearly shown that changes in lipoprotein patterns correlate with the incidence of cardiovascular disease (CVD) in that the risk of myocardial infarction increases when low-density lipoprotein (LDL) and very-low-density lipoprotein (VLDL) are elevated, and high-density lipoprotein (HDL) is lower than normal[1]. The lower susceptibility of women of reproductive age has causally been linked to the lower level of triglycerides (TG) and higher level of HDL as compared with men of equal age. As oestrogens and progestogens, particularly those of the estrane type, have been recognized to act differently upon lipoproteins (the former increasing TG and HDL and the latter having an opposite effect), oral contraceptives (OC) have been implicated as causing an increase of CVD in users[2]. The present evidence is somewhat contradictory, and it has been shown that various OCs containing different dosages of ethinyloestradiol (EE) and levonorgestrel (NG) brought about different effects upon HDL-cholesterol and the HDL-cholesterol : cholesterol ratio. It therefore appears mandatory to examine every new OC for its atherogenic potential. We are reporting here prelimi-

nary results of a study comparing the effect of two low-dose OCs upon lipoprotein patterns in young healthy women.

METHODS AND MATERIALS

Twenty-two healthy female volunteers (aged 24–35 years) with a proved ovulatory cycle participated in the study. None of the women had taken any hormonal contraceptive for at least 3 months. Preparation A was a combined, triphasic OC containing 30 μg EE and 50 μg NG (6 days), 40 μg EE and 75 μg NG (5 days), and 30 μg EE and 125 μg NG (10 days; Triquilar). Preparation B contained 30 μg EE and 150 μg desogestrel (DG; Marvelon). Eleven women were randomly assigned to use preparation A for 3 months. This was followed by a wash-out period of 3 months. Thereafter, preparation B was taken for another 3 months. This sequence was reversed in the remaining 11 volunteers. Fasting blood samples were obtained at 8.00 a.m. on days 6, 11, 21 and 28 of the (ovulatory) control cycle (C-1) preceding the first treatment cycle. This was repeated during the third treatment cycle (T-1), the third wash-out cycle (C-2), and the third treatment cycle (T-2) after the preparations had been switched.

Cholesterol (CL) (CHOD-PAP-Method, Boehringer Mannheim), triglycerides (Peridochrom Triglycerides, Boehringer Mannheim), and phospholipids (PL) (Phospholipid B-Test, WAKO Fine Chemicals, Osaka) were quantified enzymatically using commercially provided kits. HDL-CL was determined after selective precipitation of apolipoprotein B containing lipoproteins with an appropriate sodium phosphotungstate/magnesium chloride reagent[3]. Quantitative electrophoresis of lipoproteins was performed as described by Wieland *et al.*[4]. Apolipoprotein A-I[5] and apolipoprotein B[6] were determined using Mancini's single radial immunodiffusion technique with the respective monospecific antiserum.

RESULTS

Total lipid levels

The effect of a 3-month course of treatment with the two OCs is depicted in Figure 1. The open bars represent the combined mean ± SD values of the determination of CL, TG, and PL on days 6, 11, 21 and 28 in 11 volunteers taking preparation A or preparation B. There

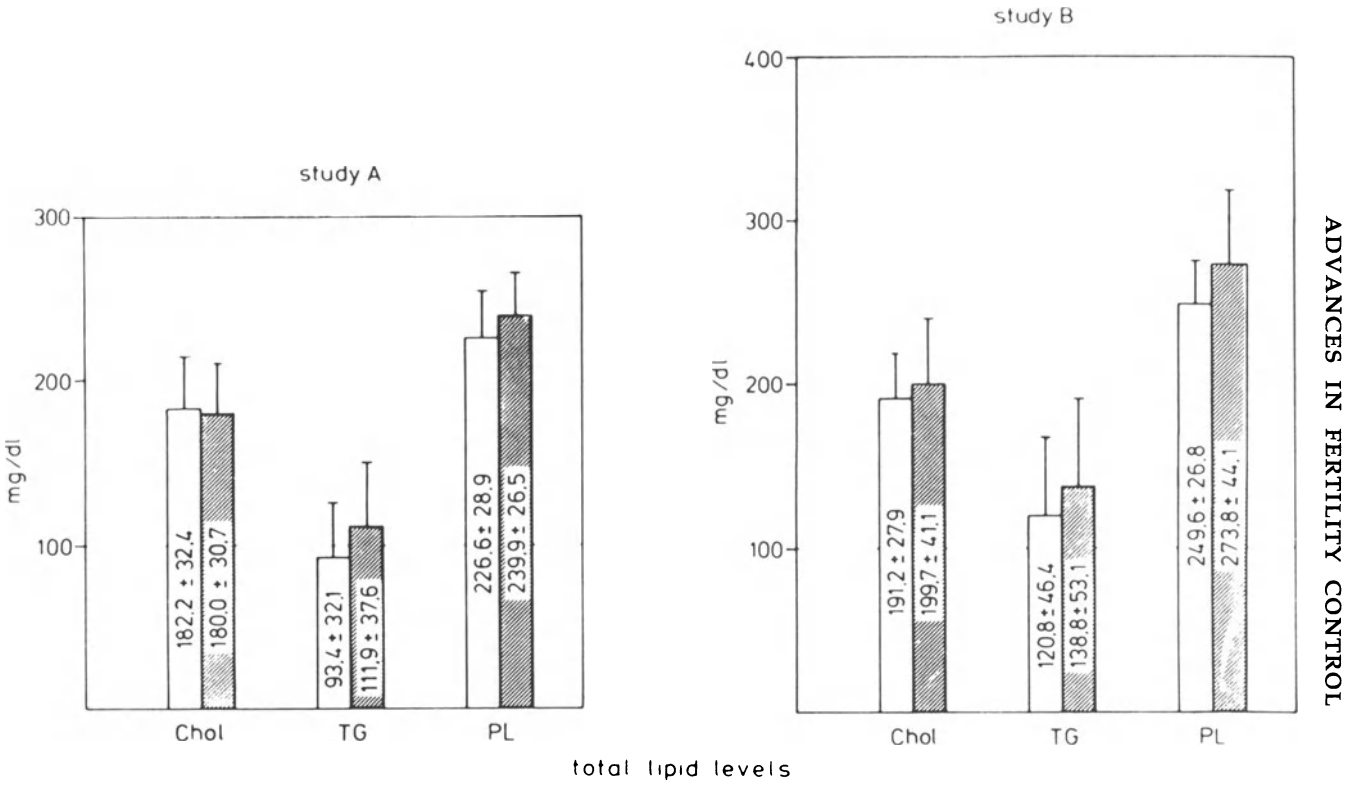

Figure 1 Total lipid levels before and during treatment with a triphasic OC (study A) and a low-dosed combined OC (study B). Open bars: mean ± SD of four assays per volunteer (n = 11) in an ovulatory control cycle. Shaded bars: values obtained during the third month of treatment.
Chol = Cholesterol; PL = phospholipid; TG = triglyceride

was no discernible effect upon total CL of either compound as compared with the control cycle. The triphasic preparation increased TG from 93.4 ± 32.1 mg dl^{-1} to 111.9 ± 37.6 mg dl^{-1} and the combined preparation brought about a rise from 120 ± 46.4 mg dl^{-1} to 138.8 ± 52.1 mg dl^{-1}. These differences were statistically insignificant. Similarly, the observed increases in plasma PL level (A = +6%; B = +10%) were of no significance.

When the data were calculated separately for days 6, 11, 21 and 28 of C-1 and T-1, no differences could be demonstrated.

Lipoprotein pattern

There was a remarkable congruence between the effects of both OCs upon plasma levels of pre-β-lipoprotein CL, β-lipoprotein CL, and α-lipoprotein CL in that there was no difference between the mean levels observed during C-1 and T-1 (Figure 2). In addition, no change in HDL-CL levels could be observed when the sodium phosphotungstate/magnesium chloride method was used.

Only apolipoprotein A-I was slightly but significantly increased ($p<0.01$) by both OCs (A = +11%; B = +16%), the increase being in each case in the same order of magnitude (Figure 3).

COMMENT

A final conclusion on the effect of the two low-dose OCs upon the lipoprotein pattern in the plasma of healthy women should not be drawn before the results of the second part of the study have become available. As each treatment period had to be limited to 3 months, changes in TG may escape detection, as this might not become noticeable before 3–6 months of treatment, as compared with a reduction in HDL which becomes demonstrable within 1 month[7]. Since the data of the first treatment period are more or less consistent with each other, it does not appear likely that major changes will be noted after the cross-over.

Whereas HDL-CL levels were not affected by either OC, a slight but significant increase of apolipoprotein A-I could be shown as compared with the control cycle. This reflects a change in the composition of HDL. This may be due in part to the relatively greater decrease of CL-rich HDL_2 density class than that of HDL_3[8]. The principle abnormality of HDL in CVD appears to be a relative decrease in the

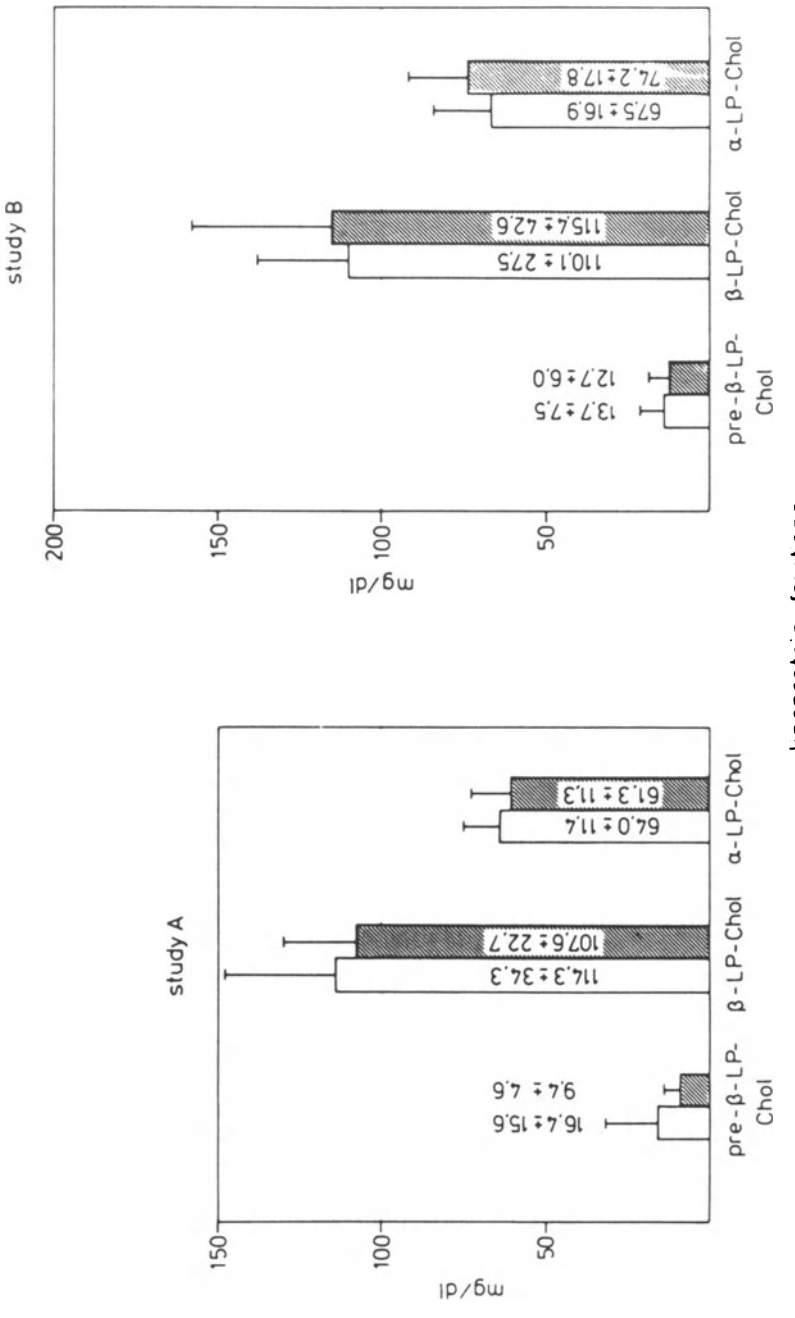

Figure 2 Lipoprotein fractions before and during treatment with a triphasic OC (study A) and a low-dosed combined OC (study B). For details, refer to legend of Figure 1

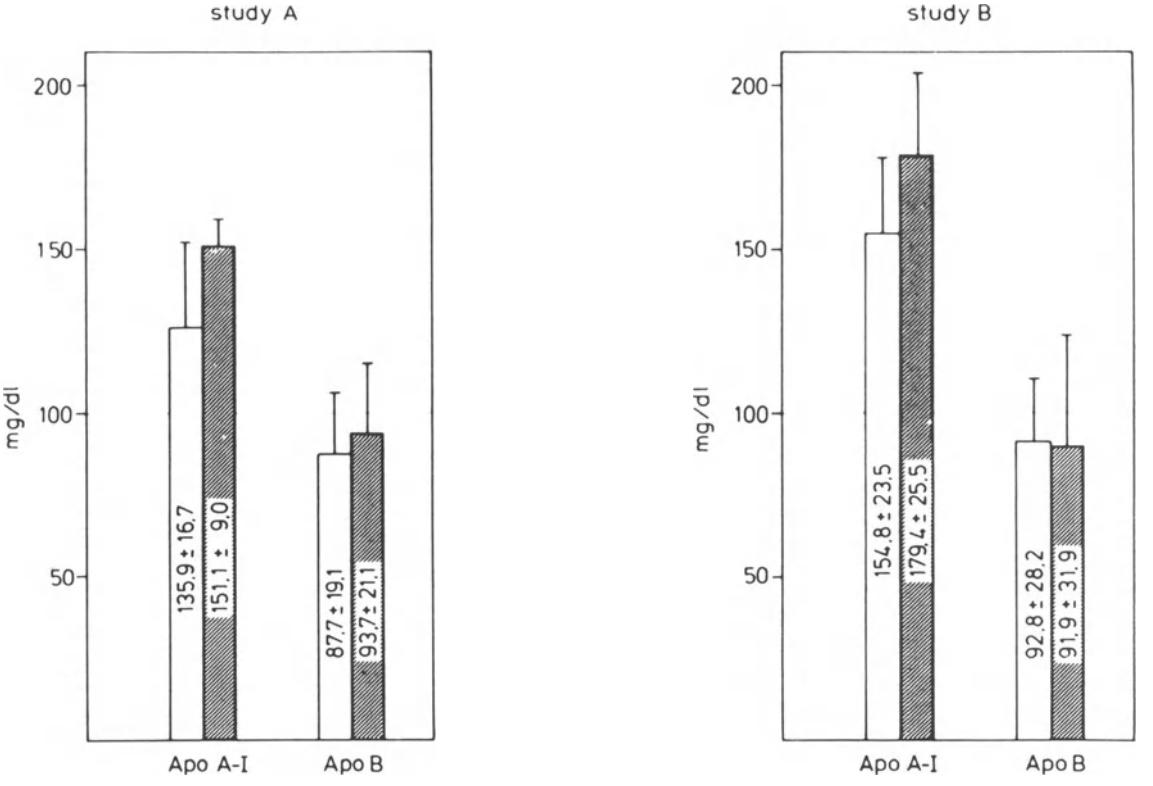

Figure 3 Apolipoprotein (Apo) A-I and B levels before and during treatment with a triphasic OC (study A) and a low-dosed combined OC (study B). For details refer to legend of Figure 1. The differences between means were of statistical significance ($p < 0.05$; Rank sum test, Mann–Whitney)

molar concentration of HDL_2 accompanied by a decrease of total HDL-CL[8,9]. Since we did not find any change in the HDL-CL concentrations, it remains to be shown whether the observed decrease in the HDL-CL : apolipoprotein A-I ratio reflects an atherogenic constellation.

It should be emphasized that the results of this study can only be considered as being representative for healthy females devoid of any disorder of lipoprotein metabolism, as such a disorder may be intensified by the use of OC[10].

We conclude that Triquilar and Marvelon do not alter lipoprotein pattern in women without risk factors in a detrimental manner; and that both preparations do not differ in this respect, even though they contain different progestogens.

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11
Carbohydrate metabolism alterations with monophasic, sequential and triphasic oral contraceptives containing ethinyl-oestradiol plus levonorgestrel or desogestrel

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INTRODUCTION

Numerous studies have shown that oral contraceptives (OCs) affect carbohydrate (CHO) metabolism and may, partly in that way, predispose to atherogenesis and vascular disease. Whereas the oestrogen component of OCs seems to produce few adverse effects on CHO metabolism, 19-norprogestogens have been shown to affect glucose tolerance adversely[1]. One of the possible mechanisms of 19-norprogestogen action could be related to a reduction in the number and/or affinity of membrane insulin receptors[2].

We investigated CHO metabolism in women receiving OCs containing low doses of 19-norprogestogens, levonorgestrel (LNg) or desogestrel (DOG) – a new 3-deoxo 11-methylene LNg derivative – to compare the potential changes observed in glucose tolerance when using these two progestogens.

SUBJECTS AND METHODS

All 38 women studied were healthy volunteers (mean age 22.75 years) within 15% of ideal body-weight, who had never used oral contraception previously or had stopped OCs at least 8 weeks prior to the study. In each individual a 3-hour, 75 g oral glucose tolerance test (OGTT) was performed at the end of a spontaneous, control cycle and again at the end of the 6th cycle of OC use. Women were allocated at random to Trigynon (n = 13), Ovidol (n = 11) or Marvelon (n = 14). Composition of the OCs is given in Table 1.

Table 1 Oral contraceptives used

Nature	*Triphasic*	*Sequential*	*Monophasic*
Trade names	Trigynon	Ovidol	Marvelon
Components and dosage	1. EE 0.03 mg+LNg 0.05 mg (days 1–6)	1. EE 0.05 mg (days 1–7)	EE 0.03 mg + DOG 0.150 mg (days 1–21)
	2. EE 0.04 mg + LNg 0.075 mg (days 7–11)	2. EE 0.05 mg + DOG 0.125 mg (days 8–21)	
	3. EE 0.03 mg + LNg 0.125 mg (days 12–21)		

EE = Ethinyloestradiol; DOG = desogestrel; LNg = levonorgestrel.

Fasting blood samples and specimens collected at 30 minute intervals during the OGTTs were analysed for blood glucose (BG), blood pyruvate (PYR), plasma immunoreactive insulin (IRI) and plasma immunoreactive glucagon (IRG). Erythrocyte insulin receptors were also measured before and after 6 months of OC use. The methods used are described elsewhere[3].

RESULTS

OGTTs

For each OC used, relative areas under mean BG, PYR, IRI and IRG curves during OGTT (3 hours) obtained during the 6th cycle of treatment have been expressed in percentage change from pre-treatment areas under the curves (AUC). Results are shown in Table 2.

Levels of BG, PYR, IRI and IRG did not differ significantly between the three groups during the pre-treatment cycle.

When comparing the three groups after 6 months of treatment (non-paired *t*-test) the AUCs (0–180 min) for BG, IRI, PYR and IRG were not statistically different. However, the AUCs for IRG were distinctly higher under DOG-containing OCs than under Trigynon treatment.

Table 2 Relative areas (as percentages of pre-treatment values at cycle 6) under mean blood glucose, pyruvate, insulin and glucagon curves during oral glucose tolerance test

	Trigynon	*Marvelon*	*Ovidol*
Blood glucose	+12*	+ 9	+ 7
Blood pyruvate	+26**	+ 2	+20
Plasma insulin	−22*	−24*	−25*
Insulin area : glucose area ratio	−31	−29	−31
Plasma glucagon	+29	+58	+62

Difference from pre-treatment mean significant, paired *t* analysis: $*p < 0.05$; $**p < 0.005$.

Insulin receptors

Erythrocyte insulin receptor levels were in the range of normal premenopausal female controls and were not influenced by OC use (Table 3).

Table 3 Percentages of binding of erythrocyte insulin receptors. Results are expressed as means ± SD

OC	*No. of patients*	*Pre-treatment cycle*	*Sixth cycle of OC use*
Trigynon	13	8.39±1.19	8.36±1.38
Marvelon	14	7.99±1.33	8.60±1.98
Ovidol	11	7.85±2.02	7.74±1.05

DISCUSSION AND CONCLUSIONS

A slight deterioration of glucose tolerance is observed after 6 months' use of the three OCs and is somewhat more obvious under Trigynon

on the basis of paired *t*-test analysis. However, BG levels never reached pathological values in any of the volunteers tested. Moreover, no statistical difference in glucose tolerance could be delineated between the three groups during the 6th month of treatment (non-paired *t*-test analysis). Blood pyruvate levels fluctuated in the same way as BG levels. Insulin responsiveness was reduced by 20% in all three groups, an observation at variance with other studies[1]. These changes could merely reflect circadian fluctuations in insulin response rather than drug-induced alterations in B-cell responsiveness, insulin sensitivity or both[4]. In the present study, we confirmed in all three groups a decrease by 30% of the insulin area : glucose area ratio at 6 months of OC use, an observation made previously by Wynn[5]. Moreover, it is noteworthy that IRG was correctly suppressed during OGTT under Trigynon but not under DOG-containing OCs. Altogether, our data indicate that the slight glucose tolerance impairment observed at 6 months of OC use is more clearly discernible for Trigynon than for Marvelon and Ovidol. In our study, glucose tolerance impairment is apparently not correlated with insulin resistance and hyperinsulinism but, in contrast, with decreased insulin secretion. Moreover, a reduction of insulin receptor number or affinity cannot be postulated to explain glucose tolerance deterioration, as insulin-receptor binding capacity remained stable during OC use in this study.

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