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Ovarian and endometrial function during hormonal contraception

The ESHRE Capri Workshop Group*

This report addresses the balance of benefits and risks from changes in ovarian and endometrial function from hormonal contraception. The main mode of action of hormonal contraception is inhibition of ovulation, due chiefly to the dose of oestrogen in combined oral contraceptives. With 20 μg dosages of ethinyl oestradiol follicular activity is more common so that contraception depends on suppression of the LH surge or disruption of the endometrial cycle. In polycystic ovary syndrome (PCOS) treated with oral contraceptives, cysts become smaller and in time the ovarian volume is reduced, ovarian testosterone secretion is reduced and there are potentially favourable effects on carbohydrate and lipid metabolism. Typical oral contraceptive users in the 1980s had a lower incidence of ovarian cysts, but modern oral contraceptives do not appear to affect the incidence of functional cysts or benign epithelial cysts. Moreover, randomized controlled trials indicate that oral contraception prescriptions are unlikely to prevent the development of functional cysts or to hasten their disappearance. Oral contraceptives, however, greatly reduce pelvic pain in women with symptomatic endometriosis and improve the health-related quality of life. Bleeding is a common response with all types of hormonal contraception, but current methodology is inadequate to make accurate comparisons of different products or of different phasic formulations. With continuing use, however, combined oral contraception is associated with endometrial atrophy, the biological plausibility for a reduced risk of endometrial carcinoma. With progestin-only contraception, a number of endometrial changes are considered as possible mechanisms of the associated bleeding but it remains largely unexplained. Oral contraceptives are frequently used for treatment of dysfunctional uterine bleeding, although only one trial has been reported. Oral contraceptive use confers protection from endometrial [relative risk (RR) 0.5] and ovarian (RR 0.4) cancers and in both cases, the protection lasts for up to 2 decades after stopping use.

Key words: cancer/endometrial function/oral contraceptives/ovarian function

Introduction

An estimated 78 million people worldwide are currently using oral contraception (14% of contraception users). An additional 16 million women use injectable or implantable methods of contraception (3% of contraception users). A total of 220 million women have ever used hormonal contraception. This paper will evaluate the known effects of hormonal contraceptive methods on ovarian and endometrial function in women during and after the reproductive years.

*A meeting was organized by ESHRE (Capri, August 23–25, 2000) with financial support from Schering S.p.A. to discuss the above subjects. The speakers included D.T.Baird (Edinburgh), J.Collins (Hamilton), I.Cooke (Sheffield), A.Glasier (Edinburgh), H.S.Jacobs (London), C.La Vecchia (Milano), G.Stock (Berlin), P.Vercellini (Milano). The discussants included J.Cohen (Paris), P.G.Crosignani (Milano), E.Diczfalusy (Ronninge), J.L.H.Evers (Maastricht), S.Skouby (Copenhagen) and B.Tarlatzis (Thessaloniki). The report was prepared by P.G.Crosignani[1] (Milano) and B.L.Rubin (Newtown Square, PA). J.Collins wrote the abstract. Professor G.Stock was a specially invited guest to provide information about the newest approaches to drug development in the field of fertility regulation.

[1]To whom correspondence should be addressed at: Department of Obstetrics and Gynaecology, University of Milan, Via Della commenda 12, 20122 Milan, Italy. E-mail: piergorgio.crosignani@unimi.it

Folliculogenesis during and after oral contraception

Combined oral contraceptive pills are composed of synthetic oestrogen (ethinyl oestradiol or mestranol) together with one of several synthetic progestogens. Their high contraceptive efficacy is due to a range of effects on the reproductive tract but their main mode of action is inhibition of ovulation. Luteinizing hormone (LH) is suppressed by both oestrogen and progestogen, which inhibits the ability of oestrogen to produce a preovulatory surge of LH (Swerdloff and Odell, 1969).

In contrast, oestrogen is mainly responsible for suppressing FSH, and hence development of follicles. Thus, the degree of follicular activity that occurs during oral contraceptive use depends on the type and dose of steroid.

Methods of studying follicular activity

Initially, determination of the activity of the ovary during oral contraceptive use depended on measurement of ovarian steroids (oestradiol and progesterone) or observation of the ovary at laparotomy (Østergaard and Starup, 1968). The introduction of high resolution ultrasound scanning by Hackeloer *et al.* (Hackeloer *et al.*, 1979) made it possible to make serial measurements of follicular growth which provided a much more accurate picture of the mode of action (Killick, 1989; Hoogland and Skouby, 1993).

Progestogen-only pills

The secretion of FSH is affected very little by natural progesterone or by synthetic progestogens used in the doses included in most oral contraceptives. Large doses of some gestogens (e.g. 10 mg norethisterone per day) suppress FSH as well as LH and, hence, follicular growth is minimal (Rudel *et al.*, 1965; Klopper, 1973). Follicular development continues during administration of progestogen-only pills and, indeed, in some, e.g. 0.30 mg norethisterone or 0.075 mg levonorgestrel, the dose is low enough so that ovulation can occur (Diczfalusy *et al.*, 1969; Landgren and Diczfalusy, 1980). Unruptured follicular cysts are common (10–20%) but are usually asymptomatic and resolve spontaneously (Tayob *et al.*, 1985). The contraceptive effect is probably dependent on the effect of continuous gestogen on cervical mucous and endometrium.

Combined oral contraception

The effect of combined oral contraceptives on follicular activity is mainly dependent on the dose of oestrogen, which has been progressively reduced from the 150 μg mestranol that was present in the original Enovid. The dose in modern low dose combined oral contraceptives (20 μg ethinyl oestradiol) is probably the minimum that will reliably suppress FSH sufficiently to prevent the growth of an ovulatory follicle. Numerous studies have demonstrated that during the 'pill free' week, there is a progressive rise in follicle growth with follicles reaching a diameter of 10–12 mm coincidental to the rise in the concentration of FSH and LH (Smith *et al.*, 1986; Elomaa *et al.*, 1998; Coney and Del Conte, 1999; Van Heusden and Fauser, 1999; Jain *et al.*, 2000). If the start of the next package is delayed by even 1 day (until day 8), there is a risk of continued follicular growth and ovulation (Killick *et al.*, 1990). The higher the dose of oestrogen, the less likely that ovulation will occur, presumably because the follicular activity is suppressed to a greater extent in the previous cycle (Grimes *et al.*, 1994). In two recent studies of pills containing 20 μg ethinyl oestradiol in combination with 100 μg levonorgestrel, follicles >10 mm diameter were seen in the majority of cycles and ovulation occurred spontaneously in 1.7–2.7% of cycles (Coney and Del Conte, 1999; Jain *et al.*, 2000). The large follicles have the potential to ovulate in response to exogenous human chorionic gonadotrophin (HCG) so that the contraceptive effect depends on suppression of the LH surge and/or disruption of the endometrial cycle (Elomaa *et al.*, 1999). The large follicles (>12 mm) found during progestogen-only pill use secrete various quantities of oestradiol, reflected in fluctuating levels of oestrogen in the peripheral blood. Although large follicles are also found, rarely, during treatment with combined oral contraceptives, these follicles secrete very little oestradiol because the concentrations of LH are usually too low to provide adequate amounts of androgen precursors for oestrogen synthesis (Crosignani *et al.*, 1996). However, these follicles may continue to secrete inhibin and may therefore be called 'functional'.

In an attempt to prevent the rise in FSH after stopping a low dose pill, one regimen involves taking 10 μg ethinyl oestradiol from day 3–7 of the 'pill-free' interval (Killick *et al.*, 1998). Whether this will result in larger numbers of women remaining amenorrhoeic or not has yet to be determined.

Biphasic and triphasic pills involving the use of varying doses of oestrogen and gestogen have been introduced in an attempt to reduce the total dose of steroid.

Polycystic ovary syndrome during oral contraceptive use

There are two main considerations when treatment with oral contraceptives is proposed for women with polycystic ovary syndrome (PCOS). The first is the effect of treatment on the ovaries and ovarian hormone secretion, the second is on the metabolic accompaniments of PCOS.

The indications to treat women with PCOS with oral contraceptives are a need for contraception, a need to protect against overstimulation of the uterus with the development of endometrial hyperplasia and cancer, a need some women have for increased cycle regularity and a need to suppress excessive androgen secretion to control seborrhoea, acne and hirsutism.

Effect of oral contraceptives on PCOS

In untreated women, polycystic ovaries are usually larger than normal with a characteristic echo pattern on ultrasound scanning. The ovaries are enlarged by a highly echodense central stroma but there are also small immature follicles (the 'cysts') of diameter 2–8 mm, usually arranged in a necklace pattern around the periphery (Adams *et al.*, 1985). On treatment with oral contraceptives the cysts become smaller. After prolonged treatment, ovarian volume decreases and the stroma becomes difficult to identify. When treatment is stopped the original PCOS picture returns, usually within a few months.

Pari passu with the above changes in ovarian dimensions, there is a reduction in the ovarian testosterone secretion rate and a fall in serum total testosterone concentrations. Depending on the oral contraceptives used, there may be a slight rise in the concentration of sex-hormone-binding globulin (SHBG), which amplifies the fall in free testosterone concentrations. Norgestrel-containing oral contraceptives, being androgenic, block the oestrogen-stimulated increase in SHBG (van der Vange *et al.*, 1990) and are unsuitable for use in women with PCOS. In terms of anti-androgenicity, oral contraceptives which contain cyproterone acetate, a specific antiandrogen is of favoured use or second line oral contraceptive with modern progestins (less partial androgenicity). With any oral contraceptive use one must remember that PCOS associated obesity is a risk factor for venous thromboembolic disease (Parkin *et al.*, 2000).

Effect of oral contraceptives on the metabolic complications of PCOS

Over the last few years there has been increasing recognition of the association of insulin resistance and compensatory hypersecretion of insulin as risk factors for the development of premature cardiovascular disease. For this reason, the effect of treatment of women with PCOS with oral contraceptives must be carefully scrutinized from the metabolic perspective. In the 1980s, Wynn's group in London studied the metabolism of hirsute women with PCOS on treatment with ethinyl oestradiol and cyproterone acetate, administered in the reverse sequential regimen. With respect to carbohydrate metabolism (Seed *et al.*, 1984), they found that in a group of >60 women the combination

of drugs reduced fasting glucose and raised fasting insulin concentrations; there was a progressive deterioration of glucose tolerance with time, together with an increased insulin response. Plasma insulin response to intravenous tolbutamide increased by 50% but without a change in the nadir glucose concentration, consistent with the development of insulin resistance. Plasma C peptide concentrations did not change, suggesting a component of the hyperinsulinaemia was caused by reduced hepatic uptake of insulin as well as increased secretion. Impaired glucose tolerance without change in insulin concentrations was detected in the phase of oestrogen-alone administration, consistent with a persisting effect of cyproterone acetate. Mild effects on carbohydrate tolerance in women using a preparation containing 35 μg of ethinyl oestradiol and 2 mg of cyproterone acetate were reported by Jandrain and colleagues (Jandrain *et al.*, 1990), although in a detailed 1 year study of seven women, using the euglycemic clamp method, Scheen and colleagues found that treatment with the same preparation did not significantly alter peripheral (presumably muscle) insulin sensitivity but did slightly increase insulin clearance (presumably by the liver) (Scheen *et al.*, 1993). The outcome of these and other more recent (Morin-Papunen *et al.*, 2000) studies indicates that adverse effects on carbohydrate metabolism depend on the dose and duration of treatment with cyproterone acetate. They suggest the dose of treatment should be progressively lowered as the benefits of treatment develop.

The effect on lipid metabolism of treatment with cyproterone acetate in the reverse sequential regimen was reported by Wynn and colleagues (Wynn *et al.*, 1986). They found that treatment with cyproterone acetate alone caused a reduction in total high density lipoprotein subfraction 2 (HDL_2) and low density lipoprotein (LDL) cholesterol. Treatment with ethinyl oestradiol alone raised triglycerides, HDL and HDL_2 and reduced LDL concentrations. The effects of the combination were also studied and the conclusion reached that cyproterone acetate had properties conventionally ascribed to both synthetic androgens (lowering HDL_2) and oestrogens (lowering LDL). Lesser effects of treatment have been reported by others (Lindberg *et al.*, 1987; Falsetti and Pasinetti, 1995) and reflect more the oestrogen than the anti-androgen component of therapy. These studies are on the whole reassuring and are consonant with the benign long-term prognosis of women with PCOS with respect to cardiovascular disease, recently reported (Pierpoint *et al.*, 1998; Wild *et al.*, 2000).

Oral contraceptive use and ovarian cysts

Ovarian cysts are usually defined as fluid-containing spaces within the ovary >30 mm in diameter. Normal ovarian follicles frequently attain 30 mm in size.

Ovarian cyst incidence is highest during the reproductive years, when oral contraceptive use is also very prevalent. Benign ovarian cysts include: (i) functional or physiological cysts arising from the follicle or the corpus luteum; (ii) benign epithelial cysts, usually of a serous or mucinous nature; and (iii) benign cystic teratomas, or dermoid cysts.

The clinical issues concern whether oral contraceptive use influences ovarian cyst incidence negatively or positively; whether the dose or formulations of the oral contraceptive preparation affect the association; and whether oral contraceptives can be prescribed to prevent or to treat follicular ovarian cysts.

Background incidence of ovarian cysts

The true incidence of ovarian cysts, including those for which hospital admission is not required, is unknown, but among 395 women evaluated on days 18–21 of a cycle prior to entering an oral contraceptive trial (median age 26 years), 44% had ultrasound evidence of 10–30 mm follicle cysts and 4% had cysts >30 mm in diameter (Teichmann *et al.*, 1995).

The incidence of hospitalization for ovarian cysts is <5 per 1000 women per annum. In one estimate, the hospitalization rate for functional ovarian cysts in the United States among women aged 15–44 years fluctuated between 472 and 522 per 100 000 women per annum in the interval from 1979 to 1986. In another estimate, mid-1980s hospital discharge rates for benign ovarian cysts in the United States and England and Wales were 131 and 67 per 100 000 women per annum respectively. Rates were highest in the third and fourth decade: 274 discharges per annum per 100 000 in the US at age 25–29 years; 142 per annum in England and Wales at age 30–34 years (Westhof and Clark, 1992). The England and Wales figures do not include private hospital admissions.

Oral contraceptive use and the incidence of functional ovarian cysts

Fewer functional ovarian cysts occurred with typical 1980s oral contraceptive use among women who were current or recent users of monophasic oral contraceptives preparations [average relative risk 0.59, 95% confidence interval (CI) 0.34, 1.02] (Vessey *et al.*, 1987; Booth *et al.*, 1992; Holt *et al.*, 1992; Lanes *et al.*, 1992).

Although the introduction of triphasic preparations did not increase hospitalization for benign ovarian cysts (Grimes and Hughes, 1989), two epidemiological studies suggest that multiphasic preparations do not reduce the risk of functional ovarian cysts (average relative risk 1.10, 95% CI 0.55, 2.21) (Holt *et al.*, 1992; Lanes *et al.*, 1992).

Oral contraceptive use and the incidence of benign epithelial ovarian cysts

In a recent review, limited data indicate that fewer seromucinous ovarian cysts occur in women who are current or recent oral contraceptive users (Chiaffarino *et al.*, 1998). In the largest study involving seven cases, the relative risk of this diagnosis for current or recent oral contraceptives users was 0.65 (95% CI 0.01, 0.90) (Vessey *et al.*, 1987).

Oral contraceptive use and the incidence of benign cystic teratomas

In two studies, only 15 benign cystic teratomas were observed among recent or current oral contraceptives users (Vessey *et al.*, 1987; Booth *et al.*, 1992). In the study with 14 cases, the relative risk for oral contraceptives users compared with never users was 1.10 (95% CI 0.01, 1.58). In the study with only one case, the relative risk for oral contraceptives users compared with never users was 0.10 (95% CI 0.01, 0.60). On

the weight of the evidence, oral contraceptives use typical of the 1980s appears to have little influence on the diagnosis of this congenital lesion.

Oral contraceptive use and the prevention of ovarian cysts

Although typical 1980s oral contraceptives were associated with a lower incidence of ovarian cysts (see above), no satisfactory evidence could be found to justify the use of any type of oral contraceptives to prevent the development of ovarian cysts. One small randomized clinical trial evaluated three 35 μg ethinyl oestradiol and norethindrone oral contraceptives among 40 volunteers during 6 months of treatment (Grimes *et al.*, 1994). The risk of developing a follicular structure >30 mm in diameter was 5.1, 10.0 and 13.3 per 100 cycles in the 1 mg, multiphasic and 0.5 mg norethindrone oral contraceptives respectively, compared with 6.7 in the non-steroidal group.

Another trial evaluated 20 μg with 150 μg desogestrel and 30 μg ethinyl oestradiol with 75 μg gestodene (Teichman *et al.*, 1995). Although there was a small and significant benefit with the 30 μg ethinyl oestradiol combination, the overall results of the two trials show that the effectiveness of oral contraceptive use for the prevention of ovarian cysts is uncertain (average relative risk 0.68, 95% CI 0.34, 1.36). The absolute treatment effect is small (0.45% fewer cysts in treated than in control cycles).

Oral contraceptive use and the treatment of ovarian cysts

The results of two small trials do not support the prescription of oral contraceptives to treat pre-existing ovarian cysts.

One small randomized clinical trial evaluated 1 mg norethindrone and 50 μg mestranol among women with functional ovarian cysts who were planning infertility treatment. The ovarian cysts regressed within 9 weeks in all women with follicle cysts averaging ⩾15 mm in diameter regardless of whether they were in the oral contraceptives group or the control group (Steinkampf *et al.*, 1990). At 6 weeks the relative risk of cyst disappearance was 1.01 (95% CI 0.06, 17.3).

Another trial evaluated low dose and high dose monophasic oral contraceptives as well as a triphasic oral contraceptives compared with expectant management (Turan *et al.*, 1994). Cysts disappeared in 52 of 55 treated patients and 16 of 17 untreated patients within 10 weeks. Although disappearance was more likely to take place in the treated groups at 5 weeks, no significant treatment effect was evident.

Combining the interim results of the two trials at 6 and 5 weeks respectively, the overall treatment effect was small and not significant. One would have to treat 16 women (95% CI 5, infinity, –15) to observe one additional cyst disappearance compared with untreated women.

An ovarian cyst appearing during oral contraceptive use is not an indication to stop oral contraceptives treatment. Such cysts are almost certain to resolve in 2–3 months. If the cyst persists after 3 months, then further investigation is indicated.

In fact, modern oral contraceptive formulations have little, if any, influence on hospitalization for functional cysts, benign epithelial cysts or benign cystic teratomas. Oral contraceptive prescriptions are unlikely to prevent the development of functional cysts or hasten their disappearance.

Oral contraceptives for the treatment of endometriosis

Conservative surgery in women with symptomatic endometriosis is generally satisfactory, but frequently with only incomplete resolution of pain or its recurrence. Repeated operations increase morbidity, yield unpredictable results even when denervating procedures are added, and may be frustrating for patients and gynaecologists (Vercellini *et al.*, 2000). When pregnancy is not an issue, medical therapies constitute a valid alternative.

The hormonal management of endometriosis is based on the presupposed response of endometriotic implants to an adverse endocrine milieu, i.e. low oestrogen and/or high progestogen or androgen concentrations. Progestogens with or without oestrogens induce anovulation and amenorrhoea according to their dosage, provoke marked decidualization, acyclicity and atrophy of eutopic and ectopic endometrium, and decrease intraperitoneal inflammation.

The clinical trials of progestogens and oestrogen-progestogens for symptomatic endometriosis reveal a consistent anti-dysmenorrheic effect of these drugs. Considering the observational studies, the frequency of non-responders at the end of treatment is ~10% (Vercellini *et al.*, 1997). To date, no comparative study has proved that the efficacy of danazol or gonadotrophin-releasing hormone analogues is superior to that of progestogens or oral oestrogen-progestogen combinations, which are similarly effective in reducing pelvic pain associated with endometriosis and in improving health-related quality of life in ~70% of symptomatic patients (Vercellini *et al.*, 1993, 1996, 1997; Gruppo Italiano per lo Studio dell'Endometriosi, 2000). The main therapeutic objective should be temporary and possibly prolonged relief of symptoms in specific circumstances and not definitive cure, because more than half of the women with severe dysmenorrhoea or deep dyspareunia will have pain recurrence within a few months of drug withdrawal whatever of the steroidal hormone used (Vercellini *et al.*, 1997; American College of Obstetricians and Gynecologists, 1999; Royal College of Obstetricians and Gynaecologists, 2000).

Progestogens are characterized by side-effects of relatively limited clinical severity, good overall tolerability, and low cost. This is particularly important in chronic diseases like endometriosis with symptoms that may disrupt working ability, social relationships, and sexual functioning. One of the main, although poorly acknowledged, problems with medical therapies for symptomatic endometriosis is the frequency and severity of side-effects caused by various drugs. This means that pain *per se* may be alleviated, but with such great disadvantages that it may be difficult to judge whether the remedy is worse than the disease.

Either alone or combined with oestrogens, as in birth control pills, progestogens might be an optimal choice for long-term treatment of symptomatic endometriosis in selected women who do not want children (American College of Obstetricians and Gynecologists, 1999; Royal College of Obstetricians and Gynaecologists, 2000). Progestogens may be preferable when

oestrogen-related metabolic and subjective side-effects should be avoided or for women with cultural or emotional objections to the use of the birth-control pill, whereas an oral contraceptive is probably the best choice to prevent the effects of oestrogen deprivation when a long period of treatment is scheduled. As pain symptoms in patients with endometriosis are mainly related to uterine bleeding episodes, continuous rather than the usual cyclic administration of oral contraceptives may be suggested.

Hormonal therapies for endometriosis are not cytoreductive and the metabolic activity of ectopic implants usually resumes after drug-induced temporary atrophy (Evers, 1987). Consequently, given the similar efficacy in pain relief of different progestogens, future research should focus more on tolerability of drugs and on dose tapering, with the aim of reducing side effects and increasing patient compliance, so that treatment periods could safely be extended.

Effects of oral contraception on vaginal bleeding

All the methods of hormonal contraception are effective, convenient and safe. The one single factor which limits their use and acceptability is bleeding dysfunction.

Bleeding patterns among combined oral contraceptive users

The combined oral contraceptive is much less likely to be associated with bleeding dysfunction than progestogen-only contraception. Most women find that the reliable cycle control conferred by the combined oral contraceptive has advantages well beyond simply providing contraception. Indeed the combined oral contraceptive is frequently prescribed for the management of menstrual bleeding disorders such as menorrhagia and dysfunctional uterine bleeding and is highly effective for these conditions. Nevertheless, cycle control is the single most important determinant of whether a new user of the combined pill will continue the method.

Bleeding disturbances during the first 3 months of use of the combined pill occur in up to 20% of cycles but tend to decrease with time. In a review of the literature (Rosenberg and Long, 1992), after 6 months of use up to 8.5% of women complain of breakthrough spotting, up to 12% complain of breakthrough bleeding and up to 6% experience amenorrhoea (absence of a withdrawal bleed). There is marked variation in the incidence of bleeding problems even for the same preparation. The risk of bleeding problems certainly depends on the dose of oestrogen in the combined pill and may possibly be related to the dose and type of gestogen. In a randomized double-blind comparison of two combined pill preparations containing the same type and dose of progestogen but different doses of ethinyl oestradiol, there was no difference in efficacy but a significant difference in cycle control (Åkerlund *et al.*, 1993).

A variety of studies have suggested that different gestogens may be associated with better cycle control. In their review, Rosenberg and Long suggested that gestodene may be better than norethindrone or desogestrel while levonorgestrel might also be better than norethindrone (Rosenberg and Long, 1992). In a more recent review (Thorneycroft, 1999), the author concluded that methodological differences between studies, particularly in terms of the definitions of bleeding and of the analysis, make it almost impossible to compare the bleeding patterns associated with one preparation or another.

Many clinicians believe that monophasic preparations may provide better cycle control than multiphasic ones. Although this would seem to be biologically plausible, this impression has not been confirmed by extensive comparative trials.

In the USA, a new tri-monthly regimen (84 days of combined pill) followed by a pill-free week is soon to be marketed. Several clinical studies have evaluated the acceptability of extended regimens of combined pill to reduce the frequency of menstruation. In a study undertaken in Edinburgh, using a high dose of combined pill, breakthrough bleeding and spotting diminished in each sequential 3 month cycle in 196 women followed up for 1 year (Loudon *et al.*, 1977). The incidence of breakthrough bleeding (BTB) decreased from 3% in 'cycle one' to 0% in 'cycle four'. Similarly spotting decreased from 24 to 4%. It makes sense to suppose that prolonged suppression of the endometrium will be associated with less BTB than if the endometrium is allowed to recover for 7 days every 4 weeks.

Although some women like the amenorrhoea associated with tricycling of the combined pill, some women who experience amenorrhoea (lack of withdrawal bleeds) with the 21 day regimen find this a worrying side effect. It is sometimes possible to reassure them that the amenorrhoea is a result simply of a particularly atrophic endometrium and therefore the absence of anything 'to bleed from'. If women are still unhappy, a regimen with higher dose of oestrogen (resulting in more endometrial proliferation) may solve the problem.

Factors which may influence cycle control on the combined pill

Compliance

Intermenstrual bleeding is most likely to be the result of missed pills. In a large study analysing the data from two multicentre trials involving over 15 000 cycles, inconsistent oral contraceptive use was associated with a 60–70% increase in the relative risk of intermenstrual bleeding (Rosenberg *et al.*, 1996).

Smoking

It has been suggested that the anti-oestrogenic effects of smoking may also affect cycle control with oral contraceptives. In a recent study of spotting and bleeding in over 16 thousand cycles of combined oral contraceptive use, the proportion of smokers reporting spotting or bleeding was significantly higher than that of non-smokers (Rosenberg *et al.*, 1996).

Effect of combined oral contraceptive on the endometrium

The low-dose combined oral contraceptive pill, exposing the endometrium as it does to continuous oestrogen and progestin, inhibits normal proliferative changes and is associated with endometrial atrophy as the progestin inhibits the effect of oestrogen on the endometrium. Specifically, the endometrium is characterized by thin, narrow, widely spaced glands and predecidual changes in the stroma. There is some evidence to suggest that a triphasic regimen is associated with less reliable

endometrial atrophy, which may give credence to the hypothesis that monophasic preparations are associated with better cycle control.

In an attempt to inhibit ovulation reliably with the lowest possible dose of steroids, without compromising efficacy while at the same time minimizing side-effects, metabolic effects and risks a new preparation has recently marketed in the USA. This comprises 21 days of 20 μg ethinyl oestradiol with 150 μg desogestrel for 21 days, followed by 2 days (22 and 23) of placebo and then 5 days of unopposed oestrogen (10 μg ethinyl oestradiol). Endometrial biopsies were taken from a small number of women in cycle 13 of use of this preparation, between days 11 and 21, and in cycle 14, between days 2 and 5 (Archer, 1999). The presence of proliferative endometrium was apparent in the days following unopposed oestrogen, but a full progestational effect was evident in all biopsies performed after 11–21 days of combined treatment.

Bleeding patterns with the progestogen-only pill

In contrast to the combined pill, the progestogen-only pill is associated with a relatively high incidence of cycle irregularity. Thirty-three percent of women who start the progestogen-only pill have some bleeding disturbance, with some 10% complaining during the first 90 days of frequent bleeding. Twenty-five percent of women using the progestogen-only pill stop during the first year because of menstrual disturbance. In contrast to the combined pill, intermenstrual bleeding and spotting tends to increase in frequency in the first 3 months of use in up to 30% of women. Although many clinicians suggest that there may be some amelioration with time, it is more likely that those women who have particularly troublesome or chaotic bleeding patterns stop using the progestogen-only pill and so the impression is one of improvement which is not borne out by research (Belsey, 1988).

While in almost all women the combined pill inhibits endogenous ovarian activity, the progestogen-only pill behaves quite differently. Some 10% to a maximum of 15% of women will have complete inhibition of ovarian activity and these women will of course be amenorrhoeic. Around 50% of women tend to have regular ovulatory cycles with a normal luteal phase and these women will have a normal menstrual bleeding pattern. The remaining 35–40% will have inconsistent suppression of ovarian activity with variable follicular development, and occasional ovulation often characterized by short or inadequate luteal phases. This latter pattern is of course a recipe for irregular bleeding. Fluctuations in circulating exogenous steroids do not however consistently correlate with breakthrough bleeding. Indeed, break-through bleeding is a side-effect whose underlying mechanisms are still poorly understood, although it is a major clinical problem.

Much of the research that has been done to investigate break-through bleeding has concentrated on long-acting low-dose progestin preparations, such as Norplant® or the levonorgestrel releasing intrauterine device, and there are virtually no data from women using the progestogen-only pill. Breakthrough bleeding probably arises from scattered areas and individual vessels rather than from the whole of endometrial surface. A number of mechanisms has been suggested (Fraser, 1999).

There is some evidence for significant change in the morphology of the endometrial vessels in women exposed to long acting progestogens. There is a reduction in numbers of the spiral arteries, sizes and the degree of spiralling. However, the main change seems to be in the capillaries and venules. Endometrial microvascular density is increased, perhaps creating more opportunities for breakthrough bleeding in women exposed to high and medium doses of progestogen. There is also evidence for an increase in the fragility of the superficial venules.

Exogenous steroids may disrupt the normal tightly controlled relationship between the growth of endothelial cells and the capillaries and the glandular and cellular components of the endometrium. Hickey and colleagues (Hickey *et al.*, 1999) have demonstrated changes in components apparently important for the structural integrity of the endothelial cell basement membrane (collagen IV, endometrial vascular laminin, and endometrial vascular heparin sulphate proteoglycan).

There may be changes in endometrial vascular constriction and dilatation and there is evidence for alterations of the synthesis and secretion of endothelin and a variety of prostanoids in the endometria of progestogen users.

Also described are substantial increases of several types of migratory leukocytes which have the potential for releasing a wide range of destructive, as well as angiogenic and repair, molecules within the endometrium.

There may be changes in endometrial haemostatic mechanisms, such as alterations in tissue fibrinolytic activity and platelet function. There may also be disturbances of mechanisms involved with endometrial repair or changes in angiogenic or endothelial growth factors.

Bleeding always follows endometrial regression, but it may be the speed of regression that determines whether bleeding occurs. Fast regression may be associated with an increased likelihood of bleeding.

All of these changes may be inter-related and may be due to a direct effect of the progestogen on the endometrium or may result from changes in the functional status of steroid receptors rendering the endometrium 'unresponsive to ovarian steroids'.

Although there have been some advances over the last 15 years in our understanding of factors which may be important in the control of endometrial function, we seem to be no nearer understanding why women on progestogen-only contraceptives suffer from breakthrough bleeding. We are certainly no nearer to finding a solution.

Oral contraceptive use in dysfunctional uterine bleeding

There are few data available on treatment of dysfunctional uterine bleeding with oral contraceptives (Hickey *et al.*, 2000; Iyer *et al.*, 2000). The current approach to evaluation of treatment requires regimens using the principles of evidence-based medicine. The results are reported in the Cochrane Collaboration database, with a randomized controlled trial (RCT) as the most powerful item of evidence. The best

evidence adduced is from Fraser and McCarron (Fraser and McCarron, 1991), in which an RCT compares a low-dose monophasic combined oral contraceptives with mefenamic acid, naproxen and low-dose danazol and measures menstrual blood loss (MBL) but there was neither a placebo nor a 'no treatment' group. The oral contraceptives group ($n = 6$) achieved a reduction of 43% in MBL ($P < 0.001$). This is the only study in the literature. A meta-analysis of other drug trials (Coulter *et al.*, 1995) provided the following percentage reductions in MBL, as given in Table I.

The clinical management of menorrhagia has been reviewed by Chuong and Brenner (Chuong and Brenner, 1996). They distinguish acute and chronic use. For an acute bleeding episode in an adolescent girl, oral medroxyprogesterone acetate (MPA) can be given for 10 days/month for ⩾3 months or larger doses for a shorter time. Oral contraceptives are helpful for chronic use in anovulatory dysfunctional uterine bleeding (the less common form) in women of reproductive age requiring contraception. When no contraception is required in this group, oral MPA or norethisterone may be given for 10 days/month for 6 months, although it offers no benefit over tranexamic acid or non-steroidal anti-inflammatory agents (NSAIDs) (Lethaby *et al.*, 2000c), In the perimenopausal woman, cyclic progestogen for 25 days or cyclic oestrogen with concomitant administration of MPA from days 16 to 25 have been suggested. A low-dose combined oral contraceptives may also be tried.

Danazol, a progestogen (also used for this indication), has significant androgenic side effects (Augood *et al.*, 2000). For long-term use, anti-fibrinolytic agents (tranexamic acid) are the first line therapy (Cooke *et al.*, 2000), having the fewest side-effects and only needing to be administered during menstrual bleeding.

The non-steroidal anti-inflammatory agents, particularly mefenamic acid, are effective, are only used during menses and can be useful for associated dysmenorrhea (Lethaby *et al.*, 2000a). The intrauterine system of levonorgestrel delivers the steroid locally and is highly effective (Crosignani *et al.*, 1997; Lethaby *et al.*, 2000b) although there is a significant side-effect of intermenstrual spotting. Amenorrhoea, which could be considered a side-effect, may be advantageous and acceptable to many women in these circumstances. Lähteenmaki *et al.* described 64% of women using such a device and removing themselves from a waiting list for hysterectomy, compared with 14% of controls (Lähteenmaki *et al.*, 1998).

Bleeding disorders such as von Willebrand's disease occur in ~1% of the population and may be treated by intranasal desmopressin acetate nasal spray.

Surgical approaches are widely used such as hysterectomy and more recently transcervical endometrial ablation (Crosignani *et al.*, 1997) or a thermal balloon. Prior to endometrial resection, the endometrium is 'thinned' to facilitate the surgery and a gonadotrophin-releasing hormone agonist or danazol may be used for this purpose (Sowter *et al.*, 2000).

Oral contraception is therefore little used for dysfunctional uterine bleeding, except for women also requiring contraception and without thrombophilic risk factors.

Long-term impact of oral contraceptives on ovarian and endometrial carcinogenesis

The protection conveyed by oral contraceptives (oral contraceptives) on ovarian and endometrial cancers is one of the most consistent epidemiological findings, and one of the most important examples—on a public health level—of a large-scale chemopreventive intervention (IARC, 1999).

An indication of the long-term favourable impact of oral contraceptives on ovarian carcinogenesis comes from descriptive epidemiology. In several developed countries, in fact, young women showed substantial declines in ovarian cancer incidence and mortality. Cohort analysis of trends in mortality from ovarian cancer indicated that women born after 1920, i.e. from the generations of mothers who had used oral contraceptives, showed consistently lower ovarian cancer rates, and the downward trends were greatest in countries where oral contraceptives were more widely utilized (La Vecchia *et al.*, 1998, 1999).

Quantification of the very long-term effect of oral contraceptives on ovarian carcinogenesis remains, however, open to discussion. While a duration effect has been reported from most studies, time since last use has been less frequently considered. The overall estimates of protection for ever-use is ~40%, and the favourable effect of oral contraceptives on epithelial ovarian cancer seems to persist for at least 10 years according to the Cancer Steroid Hormones (CASH) study, and most likely up to 15–20 years after stopping use (IARC, 1999). Thus, the relative risk (RR) was 0.6 for use stopped for ⩾10 years in a pooled analysis of European studies (Franceschi *et al.*, 1991), 0.5 for use stopped for 15 to 19, and 0.8 for ⩾20 years in a large multicentric US case–control study (Rosenberg *et al.*, 1994).

There is substantial evidence that oral contraceptive ever-use reduces the risk of endometrial cancer by ~50% (IARC, 1999; La Vecchia *et al.*, 1996), but the limited number of elderly women who had used oral contraceptives does not allow a definite estimate of the protection afforded after longer periods and/or according to duration of exposure. The reduced risk of endometrial cancer seems to persist at least 15–20 years after stopping use. In the CASH study, the RR was 0.5 for 10–14 years after stopping, in the WHO study (WHO, 1992) the odds ratio (OR) was 0.2 for high progestogen content pills ⩾10 years after stopping, in a multicentric US study the OR was 0.3 for 15–19 years and 0.8 for ⩾20 years after stopping oral contraceptives use (IARC, 1999). When duration and recency of use were evaluated jointly in a case–control study from Washington State (Voigt *et al.*, 1994), longer use (>5 years) was associated with a reduced risk, irrespective of recency. In a Swiss study (Levi *et al.*, 1991), the RR was 0.4 for 10–19 years after stopping use, and 0.8 for ⩾20 years. A population-based national case–control study from Sweden indicated that the subsequent use of hormone replacement therapy did not modify the long-term protective effect of previous oral contraceptive use (Weiderpass *et al.*, 1999).

Despite these promising results, further and more precise quantification of the possible long-term impact of oral contraceptives on ovarian and endometrial carcinogenesis remains a

major issue for any risk/benefit and public health evaluation of the pill (Gross and Schlesselman, 1994; IARC, 1999; La Vecchia *et al.*, 1999). This should be obtained by (i) further systematic re-analysis of original data from cohort and case-control studies and (ii) continued data collection, to obtain history of past oral contraceptives use in women now in late middle and elderly age.

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