Oral contraceptives

Edith Weisberg

BACKGROUND There are a plethora of different combined oral contraceptive (COC) formulations marketed in Australia, containing variable doses of ethinyloestrodiol and different progestogens, which clinically may have different effects. The number available will be further increased as new preparations are marketed.

OBJECTIVE This article aims to provide guidelines to assist general practitioners in prescribing COCs for women with different clinical conditions and needs.

DISCUSSION Although for the majority of healthy women who take COCs, any low dose combined pill will be appropriate, women with risk factors or certain conditions such as epilepsy need to be given careful consideration when prescribing. Venous thromboembolism, although rare, is the commonest serious side effect associated with COC use. The risk increases with age, obesity, smoking, and a variety of medical conditions. These women need to be advised of the risk associated with different progestogens and be involved in the decision about which pill to take.

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In prescribing the pill for an individual woman the aim should be to provide the lowest available dose of oestrogen and progestogen which gives effective contraception, produces acceptable cycle control, is well tolerated and has the least known effect on carbohydrate or lipid metabolism and haemostatic parameters.[1] Except under exceptional circumstances there is no justification for prescribing anything other than a low dose formulation containing 35 µg or less of ethinyloestradiol. The only formulations containing 50 µg ethinyloestradiol still being marketed are the biphasic levonorgestrel pill Sequilar, a 28 day pack of Microgynon 50, and the mestranol/norethisterone combined COC Norinyl-1.

Combined oral contraceptives containing the newer progestogens, desogestrel and gestodene, are considered to be an improvement on the older progestogens since they have a better metabolic profile with minimal effects on lipid and carbohydrate metabolism.[2] From a theoretical point of view, this makes them more attractive with preliminary data suggesting a possible reduction in cardiovascular disease. However, although the major risk of COC use, venous thromboembolism (VTE) has been reduced as the dose of oestrogen has been lowered, recent data have suggested that COCs containing desogestrel or gestodene carry twice the risk of VTE compared to levonorgestrel or norethisterone formulations.[3] Overall the risk of thromboembolism is very low (Table 1).[4] The absolute risk of VTE attributable to the use of COCs rises with increasing age, obesity, recent surgery, and certain forms of thrombophilia (Table 2).

All women should be given information about the risk (low) of VTE with the different progestogens in COCs[5] and also advised under what conditions to cease using COCs and use alternative methods of contraception.

Choice of pill formulation

For younger women without any special health or skin problems it probably makes very little difference which low dose oral contraceptive is prescribed. The presence of conditions such as epilepsy, acne or hirsutism, and also cost, influence the choice of pill. The cost of the newer formulations may be financially out of reach for some women. For women on social benefits generic formulations should be prescribed, as these are the only formulations subsidised under the Pharmaceutical Benefits Scheme.

For the majority of women triphasic formulations offer no benefit and may increase the likelihood of premenstrual symptoms, breast tenderness, or in a minority, dysmenorrhoea. For

Table 1. Comparative risks of thromboembolism

• nonoral contraceptive users	5/100 000 women years
• second generation oral contraceptive users	15/100 000 women years
• third generation oral contraceptive users	20-30/100 000 women years
• pregnancy	60/100 000 women years

Table 2. Risk of venous thromboembolism attributable to COC use

Risk of VTE increases under the following circumstances:

- following surgery
- following trauma
- prolonged immobilisation
- obesity
- in cancer patients
- long distance travel
- autoimmune disease
  eg. SLE, inflammatory bowel disease
- renal disease

women who develop breakthrough bleeding on low dose monophasic pills a triphasic pill may improve cycle control.

Choice of an oral contraceptive in special patient groups

History or strong family history of venous thromboembolism

It is essential when prescribing steroidal contraception that a careful medical history is taken to exclude either a personal or family history of thromboembolic disease and risk factors for VTE. Women with no risk factors for VTE may be prescribed any combined COC containing 35 µg or less of ethinyloestradiol. Women with a history of a venous thromboembolic episode should never be prescribed COC. Those with a strong family history of VTE should undergo screening to exclude thrombophilias before commencing a COC.[7] Women with a history of VTE, thrombophilias or multiple risk factors for VTE can use progestogen only methods or alternative methods of contraception.

In nonsmoking women over the age of 40 years who carry an increased risk of VTE on account of age, and especially if they are obese, it is wise to prescribe a 20 µg ethinyloestradiol/100 µg levonorgestrel combination preparation initially. If the woman develops side effects on this preparation then changing to a higher levonogestrel combination or using the third generation progestogens is warranted.[8]

To minimise the risk of VTE, women undergoing pelvic surgery or procedures requiring extensive immobilisation or the wearing of a long leg plaster should, wherever possible, cease COC use two weeks before the procedure and until six weeks after the procedure. Alternative methods of contraception should be provided during this period. The COC in nonlactating women should not be commenced until three weeks postpartum.

Adolescents

Once an adolescent has commenced menstruating COCs can be prescribed. However, it is important to take a sexual history to determine whether the young woman is at risk of sexually transmitted diseases. Adolescents should, even when the pill is an obvious choice of contraception, be given advice about safe sex practices, and advised to use a condom with a new partner even though they are using the pill for contraception. Adolescents should be prescribed a monophasic formulation as they are simpler to use. For adolescents it is particularly important to prescribe a pill which provides reasonably effective cycle control. Adolescents seem to be less tolerant of breakthrough bleeding than older women and tend to cease taking the pill if this occurs. Clinically, cycle control appears to be better with norethistrone formulations which also have a benficial effect on acne but may increase the incidence of absence of withdrawal bleeding. Women should be warned not to cease taking the pill if they have amenorrhoea until pregnancy is confirmed with a positive test. Concerns that the pill may stunt growth or affect subsequent fertility when prescribed to young adolescents are unfounded.[9]

Women with epilepsy

With the exceptions of valproate sodium and clonazepam all the older anticonvulsant drugs induce enzymes in the liver that increase the rate of

metabolism of ethinyloestradiol. Women who are using enzyme inducing drugs should use 50 µg oestrogen pills. If breakthrough bleeding occurs in the second cycle, a double dose of a 35 µg combined pill or a combination of a 30 µg and 50 µg COC can be used.[10] Despite commencing on a higher dose some women may still exhibit poor cycle control not due to other causes such as missed pills,[11] indicating inadequate protection. These women should change to an alternative method of contraception.

Women with acne

Many women find acne improves when any combined pill is used. However, a number of women find acne worsens when using a levonorgestrel formulation. For these women using a desogestrel, gestodene or cyproterone acetate formulation usually improves the condition. Women need to be warned that it may take up to six months or longer before their skin shows marked improvement.

For women who cannot afford the newer pills a formulation containing 500 µg norethisterone, which is less potent and less androgenic than levonorgestrel, usually results in improvement of acne. A generic form of this is available. The low dose tetracyclines used in the management of acne do not reduce the efficacy of the pill.[12]

For women with hirsutism the cyproterone acetate formulation is most suitable as this progestogen binds to androgen receptors blocking the action of testosterone, the cause of hirsutism. Some of the newer pills about to be marketed may also be useful.

Women over the age of 35 years

A re-analysis of data from the Royal College of General Practitioners Study in Britain has indicated that there is no increased risk of myocardial infarction for women on the pill who are nonsmokers, irrespective of age.[13] Therefore, women over the age of 35 years who are nonsmokers can use a low dose COC until the menopause. Recent studies have indicated that the mechanism of myocardial infarction in patients receiving COCs is thrombotic or due to coronary arterial spasm rather than artherosclerotic. Continuing oral contraceptive use until the menopause may have considerable benefit, as women in their 40s often develop bleeding problems either due to fibroids, adenomyosis or dysfunctional uterine bleeding.[14] The COCs offer an effective method for controlling such bleeding problems until the menopause[14] and COCs are also the best way for controlling hot flushes and other symptoms of the perimenopause, since it is often difficult to tailor hormone replacement therapy (HRT) to a woman's naturally occurring cycle.

When to cease taking the pill in a perimenopausal woman is often difficult to determine. Since the median age of menopause is around 50 years this is a reasonable age for women to change to condom use, cease taking the pill, wait for 4-6 weeks and then determine serum follicle stimulating hormone (FSH) levels.[15] If this is raised, the woman is certainly perimenopausal and may even be postmenopausal. It would be reasonably safe for her to cease contraception at this point and if she so desired change to HRT. However, HRT regimens do not provide adequate contraceptive cover. If FSH levels are within the normal range then the pill should be continued for another year and the procedure repeated.

Progestogen only pill (minipill)

For women in whom oestrogens are contraindicated, not tolerated or do not want to take a COC the progestogen only pill (minipill) is an often overlooked alternative. There are relatively few contradictions to the progestogen only pill and these include malabsorption syndromes, undiagnosed vaginal bleeding, previous ectopic pregnancy (because if pregnancy does occur with a progestogen only pill there may be a greater incidence of tubal pregnancy) and severe liver disease.[16] The progestogen only pill is taken continuously, and the major adverse effect is

Table 3. Other contraindications to COC use[6]

Existing or history of cardiovascular or cerebrovascular disease
Diabetes with circulatory problems
Complicated valvular heart disease
History of thromboembolism
Severe liver disease
Breast cancer
Uncontrolled hypertension
Focal migraine
Women >35 years smoking >15 cigarettes per day
Prolonged immobilisation
Malabsorption syndrome

unpredictable bleeding patterns. Further contraindications to COC use are listed in Table 3.

New contraceptive pills

Within the next 12-18 months it is likely that several new COCs and possibly a new progestogen only pill will be released in Australia, with a 35 µg COC contraceptive (Yasmin) containing a new progestogen, drospirenone, scheduled for release in September 2002.

Drospirenone, an analogue of spironalactone, more closely resembles natural progesterone than the nortestosterone derivatives. It counteracts the oestrogen induced stimulation of the renin/angiotensin/aldosterone system increasing sodium and water excretion.[17] It also acts as an anti-androgen, blocking the binding of testosterone to androgen receptors. Contraindications are the same as for other COCS but in addition Yasmin is contraindicated in women with kidney, liver or adrenal disease and in women taking drugs that could increase potassium retention. Preliminary studies suggest this pill could be useful in the management of women with polycystic ovarian syndrome, premenstrual syndrome, acne and weight gain due to fluid retention.[18]

Dienogest is another new progestogen which binds almost exclusively to the progesterone receptor, has anti-androgenic activity and does not bind to sex hormone binding globulin.[19] It may be available in Australia as a COC, containing ethinyloestradiol 30 µg and dienogest 2 mg (Valette). Preliminary data suggest this may be an alternative for women with loss of libido, depression or weight gain who are on other COCs.[20]

A new concept for COCs reduces the pill free gap to two days and adds five days of ethinyl-oestradiol 10 µg. Thus the cycle consists of a combined pill containing ethinyloestradiol 20 µg/desogestrel 150 µg for 21 days followed by two days of placebo pills and then five days of ethinyloestradiol 10 µg (Mircette). This should result in improved efficacy as it decreases follicle development during the usual seven day pill free interval. It does not affect cycle control or any adverse effect on the endometrium despite five days unopposed oestrogen.[21] The additional oestrogen may be helpful in the management of menstrual migraine.

Marketing approval is being sought for a progestogen only pill containing 65 µg gestodene, a dose which suppresses ovulation. Although cycle control will still be a problem with this pill efficacy should be similar to the COC providing a viable alternative for women who cannot take oestrogen.

Two other innovations which have been trialled overseas are a COC with a trimonthly cycle and an ultra low dose COC containing ethinyloestradiol 15 µg/gestodene 65 µg in 24 active pills with only four pill free days. It is uncertain whether these two preparations will be marketed in Australia. However, any monophasic pill already marketed can be used in a three monthly cycle by omitting the pill free gap.

Conclusion

The lowest dose pill which provides good cycle control and minimal metabolic changes should be prescribed. For the majority of young healthy women it makes little difference which of the low dose (<35 µg ethinyloestrodiol) monophasic combined preparations is prescribed. However, cost may be a factor and the older preparations or generics are generally cheaper.

It is important to take a careful history to determine whether risk factors for COCs exist including a strong family history for VTE. Women with such a history should be screened for thrombophilias before being prescribed COCs. Older women, especially if obese, should be prescribed a low dose levonorgestrol preparation to minimise the risk of VTE. Women on enzyme inducing drugs such as rifampicin should consider other methods of contraception. For women in whom oestrogens are contraindicated, not tolerated or do not want to take a COC, the progestogen only pill (minipill) is a good alternative.

Conflict of interest: none declared.

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SUMMARY OF IMPORTANT POINTS

- Venous thromboembolism is the commonest serious side effect associated with COC use.
- It is essential to take a careful medical history to exclude VTE when prescribing a COC.
- Women with risk factors need to be given careful consideration when prescribing a COC.
- The lowest available dose of oestrogen and progestogen should be prescribed.
- For women in whom oestrogens are contraindicated, the progestogen only pill (minipill) is an often overlooked alternative.

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