Choices in hormonal contraception

The wide range of choices now available in hormonal contraception, including new delivery systems and new progestogens, means that most women can find a hormonal contraceptive that suits their individual needs and preferences.

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The first combined hormonal contraceptives were developed nearly 50 years ago. Since that time hormonal contraception has become safer, lower in dosage, more effective and very widely used. The past 20 years in particular have seen the development of a broader range of choices, including new delivery systems and new progestogens with secondary benefits in addition to contraception.

On a sociopolitical level, the advent of hormonal contraception had enormous impact on women's reproductive choices and was a major factor in the sexual and social revolution of the 1960s and 70s. There is also no doubt that the availability and accessibility of effective contraceptive methods is largely responsible for the decline in fertility in most western countries. The present Australian fertility rate is 1.7, meaning that the average Australian woman will spend only one to four years engaged in childbearing or lactation, and will therefore have about 35 potentially fertile years where some form of contraception will be needed. A range of contraceptive options is necessary to suit the needs of different women, and even for the same woman at different stages of her reproductive life.

The first hormonal contraceptives developed contained progestogen alone, cyclical oestrogen being added later to achieve better cycle control. The contraceptive options available today still divide broadly into these two categories, and because methods within these groups share common characteristics, this is a useful way of examining them.

IN SUMMARY

- **Over the last 15 years there have been increases in the number of hormonal contraceptive preparations available and the range of systems for their delivery.**
- **A wide range of contraceptive options is required to suit the different needs of women at various stages of their reproductive life.**
- **An understanding of the properties of the various progestogens available in the combined oral contraceptive pill can assist the clinician in tailoring a preparation to best suit the individual woman's needs.**
- **The growing range of progestogen-only contraceptives represents a useful option for those women wishing to use hormonal contraception but who have medical contraindications to oestrogen or who have experienced side effects while using oestrogen-containing contraception in the past.**
- **Ready access to emergency contraception is an important public health issue. There is now good evidence that levonorgestrel emergency contraception retains some effectiveness up to 120 hours after unprotected sex and that a single-dose regimen may be preferable to the divided dose previously recommended.**

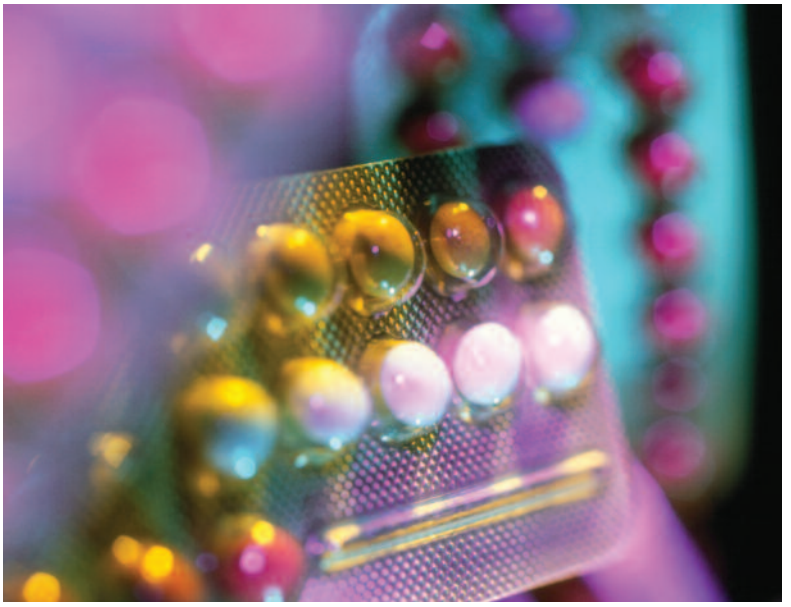

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Table 1. Risks and benefits of combined OCP use

Risks

- Unacceptable hormonal side effects
- Increased risk of thromboembolic phenomena – deep venous thrombosis and pulmonary embolus
- Increased risk of stroke – particularly in those who have pre-existing migraine with aura
- Increased risk of breast cancer (relative risk 1.24), which returns to background risk 10 years after cessation of use[1] *
- Increased risk of cervical cancer[2]

Benefits

- Highly effective contraception (failure rate of 1 to 6%) that is quickly reversible
- Reduction in menstrual disorders (PMT, dysmenorrhoea, menorrhagia); can also be used to control irregular bleeding and vasomotor symptoms around menopause[3]
- Reduction in functional ovarian cysts (less benefit with lower dose pills)[4]
- Some protection against pelvic inflammatory disease[4]
- A 50 to 60% reduction in the relative risk of ovarian and endometrial cancer, which persists 10 years after cessation of use[5]

* More recent observational studies have not, however, demonstrated this increase in risk.

Table 2. Constituents of combined OCPs available in Australia

Oestrogens

Ethinyloestradiol
Mestranol (note that 50 µg mestranol is metabolised to 35 µg ethinyloestradiol)

Progestogens

Norethisterone
Levonorgestrel
Desogestrel
Gestodene
Cyproterone acetate
Drospirenone

Oestrogen-containing contraception

Combined oral contraceptive pills

Since the first oral contraceptive pill was marketed in Australia just over 40 years ago, there has been a marked decrease in the dosage of oestrogen used and an increase in the number of available preparations. There are both risks and benefits associated with the use of combined oral contraceptive pills (OCPs; see Table 1).[1-5]

There are also some women for whom the use of oestrogen-containing contraception is an unacceptable medical risk. This includes women with previous breast or gynaecological malignancy, cardiovascular, cerebrovascular or serious liver disease, moderate hypertension, previous thromboembolism, history of migraine with aura, and women who are over 35 years of age and smoke more than 15 cigarettes a day.

Clinicians should aim to prescribe the lowest dose pill that provides effective contraception and good cycle control and causes no adverse side effects. However, there are now so many preparations available that choosing the most appropriate pill can seem a daunting task. If we examine the constituents of combined OCPs available in Australia, it can be seen that there are only two synthetic oestrogens available, and since mestranol is metabolised to ethinyloestradiol, there is effectively only one (Tables 2 and 3). It is by varying the type and dose of the wider range of progestogens available that the clinician is able to tailor the combination to suit a particular woman.

Older progestogens

Norethisterone and levonorgestrel were developed in the 1960s and 70s and contraceptive pills containing them are sometimes referred to as first and second generation pills, respectively.

Norethisterone. Norethisterone is a low potency progestogen and is fairly nonandrogenic. At the dosage required to suppress ovulation it causes very potent suppression of the endometrium, and therefore it is common for withdrawal bleeding on these pills to be very light or even absent.

Because pills containing norethisterone are relatively oestrogenic some women may experience side effects like breast tenderness, bloating and nausea.

Levonorgestrel. Levonorgestrel is a more potent progestogen than norethisterone and is more androgenic. Pills containing levonorgestrel usually provide good cycle control and reliable withdrawal bleeds. Androgenic side effects, such as irritability, weight gain and acne, can be a problem for some women.

Table 3. Combined OCPs available in Australia

Norethisterone + ethinyloestradiol
- Monophasic: Brevinor, Brevinor-1, Norimin, Norimin-1
- Triphasic: Improvil 28 Day, Synphasic 28 Day

Norethisterone + mestranol
- Monophasic: Norinyl-1

Levonorgestrel + ethinyloestradiol
- Monophasic: Levlen ED, Loette, Microgynon 20 ED, Microgynon 30, Microgynon 50, Microlevlen, Monofeme 28, Nordette 28
- Biphasic: Sequilar ED
- Triphasic: Logynon ED, Trifeme 28, Triphasil 28, Triquilar

Desogestrel + ethinyloestradiol
- Monophasic: Marvelon 28

Gestodene + ethinyloestradiol
- Monophasic: Femoden ED, Minulet 28
- Triphasic: Tri-Minulet 28

Cyproterone acetate + ethinyloestradiol
- Monophasic: Brenda-35, Diane-35 ED, Estelle-35 ED, Juliet-35 ED

Drospirenone + ethinyloestradiol
- Monophasic: Yasmin

Table 4. Managing common problems with the combined OCP

Problem	Management
Nausea	Take the pill at night after main meal Reduce oestrogen dose – e.g. reduce from 50 µg pill to 30 or 35 µg pill, or from 30 or 35 µg pill to 20 µg pill Change to progestogen-only pill
Breast tenderness	Reduce oestrogen dose – e.g. reduce from 50 µg pill to 30 or 35 µg pill, or from 30 or 35 µg pill to 20 µg pill Change to a more potent progestogen – e.g. from desogestrel or gestodene to levonorgestrel Change to progestogen-only pill
Breakthrough bleeding	Check pill taking regimen and other medications, such as antiepileptics, hypericum (St John's wort) Change progestogen – e.g. from levonorgestrel to gestodene or norethisterone Increase oestrogen dose – e.g. from 20 µg pill to 30 or 35 µg pill, or from 30 or 35 µg pill to triphasic or 50 µg pill
Missed (or very light) periods – do not neglect possible pregnancy	Increase oestrogen dose – e.g. from 20 µg pill to 30 or 35 µg pill, or from 30 or 35 µg pill to 50 µg pill Change progestogen – e.g. from norethisterone to levonorgestrel, desogestrel or gestodene
Menstrual migraine	Reduce oestrogen dose – e.g. reduce from 50 µg pill to 30 or 35 µg pill, or from 30 or 35 µg pill to 20 µg pill Use an oestradiol 50 to 100 µg/day patch during pill-free week Change to tri-monthly or continuous pill taking regimen
Bloating and fluid retention	Reduce oestrogen dose – e.g. reduce from 50 µg pill to 30 or 35 µg pill, or from 30 or 35 µg pill to 20 µg pill Change to progestogen with mild diuretic effect – e.g. to drospirenone
Decreased libido	Change progestogen – e.g. from cyproterone acetate or drospirenone to norethisterone or levonorgestrel Change to progestogen-only pill or nonhormonal method of contraception

Newer progestogens

Progestogens developed since the 1970s have been designed to be less androgenic than previously. It is now believed that all pills containing these newer progestogens (third generation pills) may be associated with a slightly higher risk of thromboembolism than those containing norethisterone or levonorgestrel.[6] This is because of their relative oestrogen dominance.

Desogestrel and gestodene. Pills containing desogestrel and gestodene generally cause fewer problems with weight gain, acne and mood alteration than those containing the older progestogens. Pills containing gestodene provide excellent cycle control.

Cyproterone acetate and drospirenone. Cyproterone acetate and drospirenone are antiandrogenic progestogens. These steroids attach to androgen receptors and prevent the action of circulating testosterone. It may, however, take several months before a clinical improvement is noted in acne or hirsuitism. In addition to its antiandrogenic action, drospirenone also has a mild diuretic effect, which can be useful in women who have previously experienced fluid retention while on the pill.

Preparations containing cyproterone acetate and drospirenone represent a new trend in oral contraception because they aim to provide additional benefits to those generally ascribed to combined OCPs.

Managing the side effects of the combined OCP

When starting a woman on the pill it is useful to consider prescribing a three- to four-month trial of a low dose preparation, with a view to adjusting the oestrogen dosage or changing the type of progestogen after that time if unacceptable side effects persist (see Table 4).

Minor problems, such as breast tenderness, nausea and irregular bleeding, are very common early on and will often settle with time. All combined pills increase the levels of sex hormone binding globulin, which means lower circulating androgen levels and the possibility of decreased libido. This side effect may be more common in women using pills containing antiandrogens such as cyproterone acetate and drospirenone.

Table 5. Progestogen-only contraceptive methods available in Australia

Short acting

- Progestogen-only pills: levonorgestrel (Microlut, Microval), norethisterone (Locilan 28 Day, Micronor, Noriday 28)

Long acting

- Intramuscular injection: depot medroxyprogesterone acetate (Depo-Provera, Depo-Ralovera)
- Contraceptive implant: etonogestrel (Implanon Implant)
- Levonorgestrel releasing intrauterine device (Mirena)
- Emergency contraception pill: levonorgestrel (Postinor-2)

Table 6. Irregular bleeding and progestogen-only contraception

Management suggestions

- Ibuprofen: 800 mg three times daily, until bleeding settles
- Tranexamic acid (Cyklokapron): 1000 mg four times daily, until bleeding settles
- Oestradiol: 2 mg daily for 21 days, either as oestradiol patch (Climara, Dermestril, Estraderm, Femtran) or tablet (Estrofem, Zumenon), or oestradiol valerate tablet (Progynova)
- Combined oral contraceptive pill: active pills for 21 days (woman will then get a withdrawal bleed)
- Progestogens: for 21 days, e.g. medroxyprogesterone acetate 5 mg (Provera, Ralovera)

Other combined hormonal contraceptives

Several alternative delivery systems, such as monthly injections, patches and vaginal rings, have been developed in recent years, although none of these are marketed in Australia yet. They have the advantages of being easier and more convenient to use than a daily pill, but all have the same contraindications, risks and benefits as oral combined preparations.

A vaginal ring known as the NuvaRing will be the first of these alternative systems available in Australia when it is released in early 2004. The hormones contained in this soft plastic ring – ethinyloestradiol and etonogestrel (the active metabolite of desogestrel) – are absorbed through the vaginal mucosa and provide three weeks of effective contraception. The ring is then removed for a week causing a withdrawal bleed, after which time a new ring is used. The very low hormone dose delivered (equivalent to 15 µg ethinyloestradiol) means that there are fewer side effects for the user – a benefit achieved without sacrificing good cycle control.[7]

Progestogen-only contraception

Contraceptive methods that contain only progestogen have the advantages of not increasing the risk of thromboembolism, stroke or heart disease, and having no significant effect on blood pressure and only minimal effects on blood lipid and glucose levels. They are, therefore, an alternative for women who wish to use hormonal contraception but have contraindications to oestrogen or who experience side effects while using it. The long acting progestogen-only methods (injections or devices) are largely user-independent, making them

particularly useful for those women who require effective contraception without the rigour of daily pill taking (Table 5).

Progestogen-only contraception does not suppress lactation and can therefore be used during breastfeeding, although depot medroxyprogesterone acetate (DPMA) is the only one of these methods licensed for this purpose in Australia.

Unfortunately, cycle control is a problem with all progestogen-only methods of contraception. Irregular bleeding is common, particularly with the long acting methods, and there is not yet an evidence based consensus on the best way to manage this. Some suggestions are given in Table 6, but if bleeding patterns remain unacceptable then there is often no alternative other than suggesting another contraceptive method.

Progestogen–only pills (minipills)

There are five progestogen-only pills available in Australia – two containing 30 μg levonorgestrel (Microlut, Microval) and three containing norethisterone 350 μg (Locilan 28 Day, Micronor, Noriday 28). These low doses mean that hormonal side effects, apart from irregular bleeding, are very uncommon.

Women using the progestogen-only pill must be meticulous pill takers since it needs to be taken within three hours of the usual time or additional contraceptive cover is required for two days. These preparations have a slightly higher failure rate than the combined pill (3 to 7%), although women with relatively low background fertility (such as those who are older or lactating) can expect lower failure rates. Since progestogen-only pills achieve maximal effectiveness between three and 21 hours after ingestion, it is best to distance taking them from the usual time of intercourse. There is also some evidence that progestogen-only pills are less effective in heavier women, so those weighing more than 70 kg should be advised to use a double dose.[8]

Depot medroxyprogesterone acetate

DMPA 150 mg (Depo-Provera, Depo-Ralovera) is a long acting method of contraception given by deep intramuscular injection every 12 weeks. It is a very effective method of contraception with a failure rate of 0.3%, and requires minimal action on the part of the user. Like all progestogen-only contraceptive methods, irregular bleeding is common initially, although there is a trend to amenorrhoea with continuing use.

There is an average delay of 10 months in the return of ovulation after cessation of DMPA so this is not really a suitable choice for women planning to fall pregnant in the near future. It may be an excellent option, however, for the older woman who has completed her family, and in whom the reduction in menstrual loss can be an advantage since this group is at more risk of dysfunctional bleeding. There are some concerns that the relative hypo-oestrogenicity experienced by long term users of DMPA could adversely affect bone density, and some authorities recommend bone densitometry after five years of use.[9]

Contraceptive implant

Implanon, the only contraceptive implant available in Australia, is a single rod implant designed to provide contraceptive cover for up to three years.[10] It releases 60 μg of etonogestrel per day initially but this decreases to 30 μg per day by the end of the third year. This is sufficient to suppress ovulation and the method has a failure rate of less than 1%. Because follicular activity is not completely suppressed, oestrogen levels remain adequate for maintenance of bone density. It is quickly reversible, with most women ovulating within one month of the device being removed.

As with all progestogen-only methods, the main problem with Implanon is the irregular bleeding pattern experienced by users, which can span from amenorrhoea to almost constant light bleeding. This pattern is usually established by four to five months of use and if it proves to be unacceptable to the woman, it is usually suggested that the implant be removed. Between 15 and 20% of women will have the implant removed in the first 12 months of use. Implanon may be a useful option in adolescents, who are notoriously poor oral contraception pill takers, but it is important to recognise they will also be less tolerant of irregular bleeding.

Levonorgestrel releasing intrauterine device

The levonorgestrel releasing intrauterine device (IUD) Mirena releases about 20 μg of levonorgestrel a day within the uterine cavity.[11] The device has a lifespan of five years and is extremely effective, with a failure rate of 0.2%. The effect is mainly local, with circulating hormone levels being equivalent to about two minipills a week, and because of this systemic side effects are rare.

The device works mainly by making the endometrium unsuitable for implantation and by thickening the cervical mucus so that sperm find it difficult to penetrate. There is some inhibition of ovulation in the first 12 months of use, but after that time most women ovulate normally, so it may not be a particularly good choice for those women with severe premenstrual symptoms. The suppressive effect on the endometrium means that, unlike a copper-bearing IUD, Mirena reduces the amount of menstrual loss with time, although irregular bleeding is very common in the first five months of use. It is, therefore, a very suitable contraceptive choice for the older woman or those with heavier menstrual bleeding, and can be used as the progestogen component of hormone replacement therapy around menopause. There is an immediate return to background fertility once the device is removed.

Emergency contraception

Progestogen-only emergency contraception has been shown to have fewer side

effects and to be more effective than the older Yuzpe combined oestrogen–progestogen method, making it the method of choice for emergency contraception. It can prevent 85% of the pregnancies expected from mid-cycle sex. The first commercial emergency pill preparation, Postinor-2, became available in Australia in 2002, and has recently been approved as a pharmacist-supplied item. There are virtually no contraindications and no significant complications associated with its use.

Traditionally, the recommendation has been that the method should consist of two doses of 75 μg levonorgestrel taken within 72 hours of unprotected sex. However, a large study published in late 2002 demonstrated that the method retained some effectiveness up to 120 hours, and that two tablets taken at once (150 μg) appeared slightly more effective than the divided dose.[12] Compliance is also greatly increased with this alternative regimen, and many practitioners are now recommending it.

Conclusion

Modern hormonal contraception is both effective and safe. The wider range of choices now available means it should be possible for most women to find hormonal contraceptive methods that suit individual needs and preferences. MT

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DECLARATION OF INTEREST: Dr Foran has been involved in developing and delivering educational programs and consumer product information for Wyeth, Schering and Organon. FPA Health has a research function that is actively involved in clinical trials of new contraceptive methods.