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Hormonal contraceptives: tailoring for the individual

More than one-third of Australian women aged between 16 and 60 years use some form of hormonal contraceptive.¹ With new products continually emerging on the market, health practitioners may find it difficult to keep up to date. This *NPS News* explores the range of hormonal contraceptives currently available in Australia and factors to consider when initiating or modifying prescribing.

Benefits of hormonal contraceptives

Hormonal contraceptives are very effective and have given women unprecedented fertility control. Most have well-defined safety profiles because of their long and widespread use. There are also some non-contraceptive health benefits associated with certain hormonal contraceptives. These include reduced risks of ovarian and endometrial cancers, benign breast disease and menstrual cycle disorders.²⁻⁷

- comorbidities (e.g. metabolic syndrome, obesity, menstrual disorders, acne, etc — see page 2)
- risk factors for cardiovascular conditions or cancer (see page 3).

When appropriate, discuss hormonal contraceptives in the context of sexual health and remind patients about safe sex practices.

Choosing the right hormonal contraceptive

Hormonal contraceptives encompass a variety of oestrogen/progestogen and progestogen-only formulations, delivered in several ways (see Table 1). Discuss the advantages and disadvantages of each modality with individual patients (Table 1), taking into account:

- age (give special consideration for adolescents and women over 35 — see page 2)
- risk for sexually transmitted infections
- adherence issues
- parity
- time frame for returning to fertility after contraceptive use
- suitability when breastfeeding
- smoking (see page 2)
- regular use of enzyme-inducing drugs or complementary medicines (e.g. St John's wort)

Long-term hormonal contraception

For women seeking long-term contraception, four long-acting methods are available:

- etonogestrel implant (Implanon)
- levonorgestrel-releasing intrauterine device (IUD; Mirena)
- depot medroxyprogesterone acetate (DMPA) injection (Depo-Provera)
- ethinylloestradiol/etonogestrel-releasing vaginal ring (NuvaRing).

These methods are effective and, except for the vaginal ring, are relatively independent of user adherence. Consider the merits of each of the long-acting contraceptives (see Table 1 and page 4) and individual suitability (Figure 1) — see insert.

NPS is an independent, non-profit organisation for Quality Use of Medicines, funded by the Australian Government Department of Health and Ageing.

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Hormonal contraceptives in special circumstances

Adolescents

Discuss the potential and perceived non-contraceptive effects of hormonal contraceptives (e.g. reduced premenstrual symptoms, regular menstruation, weight gain, headaches, etc.) with adolescents. As appropriate, prescribe a low-dose (20 microgram ethinyloestradiol) monophasic combined oral contraceptive.⁸ Consider an implant or vaginal ring if adherence is likely to be a problem. Provide counselling about safe sex.

Women with cardiovascular risk factors

Cardiovascular risk is an important consideration in choosing an appropriate hormonal contraceptive. Combined oral contraceptives increase cardiovascular risk in women who have one or more cardiovascular risk factors including:

- smoking, in women over 35
- obesity (body mass index > 30 kg/m²)
- uncontrolled hypertension, hyperlipidaemia or diabetes with vascular disease
- family history of cardiovascular disease before age 50.^{9,10}

Consider non-hormonal or progestogen-only methods (progestogen-only pill, DMPA, etonogestrel implant or levonorgestrel-releasing IUD) first in such women.

Women over 35

For women over 35, consider non-hormonal or progestogen-only methods first if there are other cardiovascular risk factors.⁸⁻¹⁰ Combined oral contraceptives can be used by women over 35 without cardiovascular risk factors.⁹

Missed pills and emergency contraception

If an active combined oral contraceptive pill has been missed, the missed pill should be taken as soon as possible and the remaining pills should be taken as usual. If the active combined oral contraceptive pill has been missed by > 24 hours, an additional method of contraception is needed or intercourse should be avoided for 7 days. Consider emergency contraception if the missed pill was from the first 7 days of the pack and the woman had unprotected intercourse in the previous 5 days.⁹ If the missed pills were in the week before the inactive pill or pill-free week, the woman

Metabolic syndrome or diabetes

Consider non-hormonal contraceptives first in women with metabolic syndrome, as they have multiple cardiovascular risk factors.¹¹ Hormonal contraceptives can generally be prescribed in non-smokers who have diabetes without nephropathy, retinopathy or neuropathy, although evidence is limited.^{10,12,13}

Smokers

Combined oral contraceptive use in heavy smokers substantially increases cardiovascular risk.^{10,14}

Use of enzyme-inducing drugs

Hepatic enzyme-inducing drugs (e.g. phenobarbitone, phenytoin, carbamazepine, oxcarbazepine, topiramate, rifampicin, griseofulvin and St John's wort) can interact with hormonal contraceptives and reduce their efficacy. Consider other contraceptives first (e.g. levonorgestrel-releasing or non-hormonal IUD or DMPA). Alternatively, tri-cycle* combined oral contraceptives (containing 50 microgram ethinyloestradiol) with a 4-day pill-free period after each 3-packet cycle.⁹ Etonogestrel implants are not recommended for patients on hepatic enzyme-inducing drugs.^{15,16}

Menstrual disorders

(Menorrhagia/dysmenorrhoea)

Initiate therapy with a monophasic combined oral contraceptive. If menorrhagia or dysmenorrhoea remains uncontrolled, tri-cycle pills to reduce the frequency of withdrawal bleeding.¹⁷ The levonorgestrel-releasing IUD is an alternative for managing menorrhagia.⁹

* 'Tri-cycling' involves continuous use of active pills for 2 months and only having an inactive pill or pill-free period in the 3rd month.

should finish the active pills in the current pack and begin with the active pills in the next pack (i.e. skip the inactive pills or pill-free week).¹⁷

If a progestogen-only pill has been missed by > 3 hours, the missed pill should be taken as soon as possible. An additional method of contraception is needed or intercourse should be avoided for 2 days (i.e. until 3 consecutive pills have been taken). Consider emergency contraception if the woman had unprotected intercourse during these 2 days.⁹

Adverse effects

Managing minor adverse effects

Adverse effects are often cited as reasons for discontinuation of hormonal contraceptives and occur across the oestrogenic to progestogenic spectrum.^{18,19} The more common, relatively minor adverse effects can be managed by modifying the oestrogen and/or progestogen dose or type (see insert, Table 2) as long as the change does not increase the risk for more serious medical conditions.

Cardiovascular risks

Venous thromboembolism

Combined oral contraceptive users have a higher than baseline risk of venous thromboembolism (Table 3) but, as this is rare among reproductive-aged women, the absolute risk is small. Third-generation progestogens (desogestrel or gestodene) may further increase the risk of venous thromboembolism (Table 3) but the risk associated with pregnancy is higher.²⁰⁻²³

Table 3: Risk of venous thromboembolism among combined oral contraceptive users⁵⁸

Comparator	Absolute risk (per year per 100,000 women)	Relative risk
Not using combined oral contraceptive	5	BASELINE
Combined oral contraceptive with levonogestrel or norethisterone	15	3-fold increase
Combined oral contraceptive with gestodene or desogestrel	25	5-fold increase
Pregnancy	60	12-fold increase

Note: Risk of venous thromboembolism using combined oral contraceptive with drospirenone (Yasmin) is similar to that of other combined oral contraceptives.^{59,60} Risk of venous thromboembolism using combined oral contraceptive with cyproterone acetate (e.g. Diane-35 ED) was reported to be 4-fold higher, compared with combined oral contraceptive with levonogestrel.⁶¹

Other factors that increase risk of venous thromboembolism include:

- age²⁴
- obesity²⁴
- high oestrogen dose²³
- smoking²⁴

- prothrombotic conditions (e.g. thrombogenic mutations, immobilisation following major surgery)^{9,10}
- a family history of venous thromboembolism.^{9,10}

Venous thromboembolism risk is highest in the first year of combined oral contraceptive use, particularly in women with thrombogenic mutations.^{23,25}

Myocardial infarction and ischaemic stroke

Choose hormonal contraceptives based on overall cardiovascular risk (see above), as this is the primary determinant of myocardial infarction and stroke risk in reproductive-aged women.²⁶

Myocardial infarction and stroke are uncommon in non-smoking reproductive-aged women and there is only weak evidence that low-dose combined oral contraceptive use increases the risk of myocardial infarction and ischaemic stroke.^{14,27-32} In studies that found an association, the absolute risks with combined oral contraceptive use were low — an estimated 3 extra cases of myocardial infarction per year per 100,000 non-smoking women over 35, and 4.1 extra cases of ischaemic stroke per year per 100,000 non-smoking, normotensive women.^{28,30} The presence of other cardiovascular risk factors substantially increased the risk of both conditions.^{14,28,29,31,32} Hormonal contraceptives can increase the risk of ischaemic stroke in women who suffer migraines with aura; consider progestogen-only or non-hormonal methods of contraception for these women.^{33,34}

Cancer risk

Breast cancer

The small increase in risk of breast cancer in combined oral contraceptive users appears to revert to no excess risk 10 or more years after discontinuation.³⁵ In practical terms, any excess risk may not be clinically significant, as the incidence of breast cancer is much higher later in life. Indeed, a meta-analysis found little difference between users and never-users in the calculated cumulative number of breast cancers for women up to the age of 50.³⁵

Cervical cancer

Current or recent use of hormonal contraceptives may slightly increase the risk of cervical cancer.^{36,37} However, the evidence is inconsistent and the effects of other potentially confounding factors, such as sexual behaviour and persistence of human papillomavirus infection, remain unclear.³⁸⁻⁴⁰

Adverse effects of non-oral hormonal contraceptives

Most of the evidence on adverse effects and serious risks with hormonal contraceptives comes from observational studies. There is less evidence about long-term risks for the other methods. Nonetheless, as these methods also involve the administration of exogenous steroid hormones, the same general principles apply as for prescribing oral contraceptives.

Menstrual disturbances are common with progestogen-only methods. Usually this will manifest as amenorrhoea or infrequent short bleeds, but frequent and/or prolonged bleeding can occur in a minority of users. Counsel all women considering progestogen-only methods about menstrual disturbances before use.

Etonogestrel implant (Implanon)

Menstrual disturbances are a reason for discontinuation in up to 21% of etonogestrel implant users.^{41,42} Menstrual disturbances are most likely during the first 3–6 months but may stabilise later.⁴¹ The implant may also be associated with acne.^{15,41}

Doctors must attend a training course before inserting or removing etonogestrel implants. Improper insertion can lead to implant expulsion and/or contraception failure. Also, if the implant is inserted too deeply it may be difficult to remove.

Levonorgestrel-releasing IUD (Mirena)

Menstrual disturbances are also common with the levonorgestrel-releasing IUD.^{43–45} In an open-label study (N = 678) the cumulative event rate over 5 years for menstrual disturbances was 16.7%.⁴³ Other potential problems include expulsion (5.9%) pain (4.3%) and functional ovarian cysts (12%), which spontaneously regress.^{43,46}

The absolute risk of ectopic pregnancy with this method is low and is less than when using no contraception.¹⁵ However, in the case of contraception failure, consider the possibility of an ectopic pregnancy.⁴⁶

Depot medroxyprogesterone acetate (DMPA) injection (Depo-Provera)

Menstrual disturbances and weight gain are common reasons for discontinuation of this method.^{47,48} Amenorrhoea can be expected in 50% of users after 12 months and 70% of users after 24 months.⁴⁹

Loss of bone mineral density is the most significant risk associated with DMPA injections. This is particularly important in adolescents and very young women, who may not have reached their peak bone mass, and older women with risk factors for osteoporosis.^{50–52} In most women bone mineral density returns to normal levels on discontinuation of DMPA.⁵³ Consider other methods first for long-term (i.e. > 2 years) contraception in these age groups.⁵²

Ethinylloestradiol/etonogestrel-releasing vaginal ring (NuvaRing)

In a 1-year study, the incidence of break-through bleeding or spotting with the combined vaginal ring was comparable to that with drospirenone-containing combined oral contraceptives.⁵⁴ Vaginitis and vaginal discharge were more frequently reported by women who used the combined vaginal ring than by combined oral contraceptive users.^{55,56}

Useful Resources

Consumer medicine information leaflets (http://www.nps.org.au/site.php?page=2&content=/resources/content/cmi_search.php)

Faculty of Family Planning and Reproductive Health Care of the Royal College of Obstetricians and Gynaecologists (<http://www.ffprhc.org.uk>)
Family Planning NSW (<http://www.fpahealth.org.au>)

National Institute of Health and Clinical Excellence Long-acting Reversible Contraception guidelines (<http://guidance.nice.org.uk/CG30/?c=91520>)

WHO Medical Eligibility Criteria for Contraceptive Use (<http://www.who.int/reproductive-health/publications/mec/index.htm>)

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The information contained in this material is derived from a critical analysis of a wide range of authoritative evidence. Any treatment decisions based on this information should be made in the context of the clinical circumstances of each patient.



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Table 1: Hormonal contraceptive types, failure rates, risks and additional indications

Type and components	Trade names	First year failure rate* (%)	Advantages/additional indications	Disadvantages/potential side effects/risks
Combined oral		Typical use: 8 Perfect use: 0.3	Highly effective, easily reversible contraception. Non-contraceptive health benefits (e.g. reduced risk of ovarian and endometrial cancer, benign breast disease, etc)	Dosing: Must be taken daily regardless of frequency of intercourse (see also <i>Adverse effects</i> , page 3)
Ethinylestradiol/levonorgestrel	Levlen, Loette, Logynon, Microgynon series, Microlevlen, Monofeme, Nordette, Trifeme, Triphasil, Triquilar		Loette: indicated for moderate acne	—
Ethinylestradiol/gestodene	Femoden, Minulet		Less androgenic than levonorgestrel formulation	Increased risk of venous thromboembolism
Ethinylestradiol/desogestrel	Marvelon 28		Less androgenic than levonorgestrel formulation	Increased risk of venous thromboembolism
Ethinylestradiol/cyproterone acetate†	Brenda-35, Diane-35, Estelle-35, Juliet-35		Anti-androgenic: only indicated for severe acne or moderate hirsutism†	Increased risk of venous thromboembolism
Ethinylestradiol/norethisterone	Brevinor, Improvil 28 Day, Norimin, Synphasic		—	—
Ethinylestradiol/drospirenone	Yasmin		Anti-androgenic: indicated for moderate acne	Potential for hyperkalaemia in women with renal impairment or those taking potassium-sparing drugs; limited data on venous thromboembolism risk.
Ethinylestradiol/dienogest	Valette		Anti-androgenic: indicated for moderate acne	
Mestranol/norethisterone	Norinyl-1		—	—
Progestogen only oral		Typical use‡: 8 Perfect use‡: 0.3	—	Dosing: Must be taken at approximately the same time each day regardless of frequency of intercourse
Levonorgestrel	Microlut			
Norethisterone	Locilan 28 Day, Micronor, Noriday 28			
Emergency oral, levonorgestrel	Levonelle-2, NorLevo, Postinor-2	[see footnote]‡	Emergency contraception, ideally to be used within 72 hours (but up to 120 hours) of unprotected sex	Nausea, vomiting (rare)
Implant, etonogestrel	Implanon	Typical use§: 0.05 Perfect use§: 0.05	Duration of action: effective for 3 years	Minor surgical procedure needed to implant or remove; not recommended for concomitant use with enzyme-inducing drugs; menstrual disturbances, amenorrhoea; acne
Injection, medroxyprogesterone acetate	Depo-Provera, Depo-Ralovera	Typical use: 3 Perfect use: 0.3	Duration of action: effective for 3 months	Delay in return to fertility (average 6 months); menstrual disturbances, amenorrhoea; weight gain; may be associated with a largely reversible loss in bone mineral density. Black box warning by US FDA and WHO-MEC Category 2** for < 18 and > 45 year olds based on bone mineral density effects
Intrauterine device, levonorgestrel-releasing	Mirena	Typical use: 0.1 Perfect use: 0.1	Duration of action: effective for 5 years. Additional indication: idiopathic menorrhagia	Menstrual disturbances, amenorrhoea; expulsion; perforation of uterus; pain; acne
Vaginal ring, ethinylestradiol/etonogestrel-releasing	NuvaRing	Typical use¶: 8 Perfect use¶: 0.3	Duration of action: ring remains in vagina for 3 weeks then removed for 1 week. Inserted and removed by user	Vaginal discharge, vaginitis, irritation. User must remember to remove, and re-insert after ring-free week Limited data on venous thromboembolism risk

* % of women experiencing an unintended pregnancy in the first year of use.⁵⁷

† Not indicated for contraception alone.

‡ Estimated 85% reduction in risk of pregnancy after a single act of unprotected sex

§ Figures based on levonorgestrel implant (Norplant), which is not available in Australia.

¶ Based on combined data for combined oral contraceptive and progestogen-only pills. The effectiveness of the progestogen-only pill may be lower as it is less likely to be taken perfectly. There are no data for the vaginal ring — it is assumed that it is no less effective than oral contraceptives.

** WHO Medical Eligibility Criteria Category 2: A condition where the advantages of using the method generally outweigh the theoretical or proven risks.¹⁰

Table 2: Managing common adverse effects of combined oral contraceptives^{8,9}

Adverse effect	Action needed	Examples of pill change
Acne	Reduce or change progestogen to a less androgenic formulation	Microgynon 30/Brevinor to Diane ED/Marvelon
Amenorrhoea	Increase oestrogen or decrease progestogen	Nordette/Microgynon 30 to Microgynon 50
Breakthrough bleeding <ul style="list-style-type: none"> early to mid cycle late cycle 	Increase oestrogen Increase progestogen or change type	Microgynon 30/Brevinor to Microgynon 50 Triphasil to Nordette Nordette to Norinyl-1
Breast problems <ul style="list-style-type: none"> fullness/tenderness mastalgia 	Decrease oestrogen Decrease progestogen	Microgynon 30/Brevinor to Microgynon 20 Nordette/Microgynon 30 to Triphasil/Triquilar
Chloasma	Stop oestrogen Try progestogen-only pill Avoid direct sun (use sunscreen)	
Depression	(No evidence to guide management, pill change may help)	
Headache <ul style="list-style-type: none"> migraine with aura in pill-free week 	Discontinue pill Add oestrogen daily during pill-free week Tri-cycle pills to avoid the pill-free week	
Libido loss	(No evidence to guide management, pill change may help)	
Nausea/vomiting	Decrease or change oestrogen or stop oestrogen or take pill at night	Change to Microgynon 20, Loette or progestogen-only pill
Weight gain <ul style="list-style-type: none"> constant cyclic 	Decrease or change progestogen Decrease oestrogen	Nordette/Microgynon 30 to Brevinor or Marvelon Microgynon 30/Brevinor to Microgynon 20

Figure 1: Suitable candidates or conditions across the oestrogenic to progestogenic spectrum of oral contraceptives (A) and for the long-acting contraceptives (B).

