[X] Close

Classification of contraceptive methods

Classification of contraceptive methods

Contraceptive methods can be classified by their mechanism of action (eg hormonal versus nonhormonal) or duration of action (eg long acting versus shorter acting). This guideline covers:

- long-acting reversible contraception (LARCs)
  - intrauterine contraceptive devices (IUDs)—levonorgestrel-releasing and copper intrauterine IUDs
  - etonogestrel contraceptive implant
- shorter-acting hormonal contraception
  - depot medroxyprogesterone injection
  - combined hormonal contraception—combined oral contraceptives (COCs) and the contraceptive vaginal ring
  - progestogen-only contraceptive pills
- barrier methods of contraception—male (external) and female (internal) condoms, diaphragm
- sterilisation—vasectomy and tubal sterilisation
- other contraceptive options—fertility awareness methods, lactational amenorrhoea method and withdrawal method
- emergency contraception—oral emergency contraception, copper IUD.

The classification of hormonal contraceptives is described in Table 20.1.

Table 20.1 Classification of hormonal contraceptives

Progestogen-only contraceptives	
long-acting	levonorgestrel-releasing intrauterine contraceptive devices (LNG-IUDs)
	etonogestrel contraceptive implant
shorter-acting	depot medroxyprogesterone injection (DMPA)
	progestogen-only contraceptive pills (POPs)
Combined hormonal contraceptives	
shorter-acting	combined oral contraceptives (COCs)
	contraceptive vaginal ring

Overview of factors affecting contraceptive choice

Overview of factors affecting contraceptive choice

Contraceptive choice is influenced by multiple factors. Medical practitioners must ensure the safety of the method for the individual's situation, and support informed decision-making based on patient preference.

Contraception may be relevant to all individuals, regardless of gender identity. Conception may be possible for anyone presumed female at birth (this includes cis women, trans men and some nonbinary individuals). Contraception may also be relevant to anyone presumed male at birth (this includes cis men, trans women and some nonbinary individuals). See Trans and gender diverse health for more information on terminology.

Factors influencing contraceptive choice include:

- contraindications and precautions (see Medical eligibility criteria for contraceptives), and adverse effects of the method
- potential for drug interactions
- effectiveness of the contraceptive method and consequences of unintended pregnancy
- need for immediate start (including Quick Start of hormonal contraceptives)
- reproductive stage of life
- timeframe for planned pregnancies—return of fertility may be delayed with depot medroxyprogesterone injection
- mechanism of action—a method that does not prevent implantation or ovulation may be preferred for religious or cultural reasons
- reversibility
- noncontraceptive benefits, such as improvement in acne, dysmenorrhoea or heavy menstrual bleeding with some hormonal contraceptives
- need for a discreet method of contraception (eg for young people or anyone experiencing pressure to avoid contraception against their will)
- risk of sexually transmitted infections—discuss use of condoms as part of a dual-method approach to contraception
- cost and accessibility.

Long-acting reversible contraception is the most reliable and cost-effective reversible method of contraception.

If reliability and cost effectiveness are paramount, long-acting reversible contraception (LARC) is an appropriate choice for females of all ages. LARCs include the etonogestrel subcutaneous implant, levonorgestrel-releasing intrauterine contraceptive devices (LNG-IUDs) and copper IUDs. Misinformation and misperceptions about adverse effects and contraindications of LARCs are common; ensure awareness of the available LARC methods and their ease of use, efficacy and safety, including in young nulliparous individuals.

Intrauterine contraceptive devices can be safely used by young nulliparous individuals.

Medical eligibility criteria for contraceptives

Medical eligibility criteria for contraceptives

Medical Eligibility Criteria (MEC) is a globally recognised system used to classify the contraindications and precautions for contraceptives. It provides evidence-based guidance on which methods of contraception may be used safely by individuals with specific medical conditions or characteristics. This guidance may differ from the product information. The United Kingdom Medical Eligibility Criteria (UKMEC) is the system most applicable to the Australian setting.

Definitions of the UKMEC categories are listed in Table 20.2. For full details of UKMEC categories of each contraceptive method for specific conditions, see the Faculty of Sexual and Reproductive Healthcare website.

In this topic:

- UKMEC 1 or UKMEC 2 categories are described as ‘safe to use’
- UKMEC 3 categories require expert clinical judgment or referral
- UKMEC 4 categories are absolute contraindications.

For individuals with multiple conditions, clinical judgment is required to determine medical eligibility because the UKMEC categories consider each condition in isolation only.

For some conditions, the UKMEC varies depending on whether the method of contraception is being started or continued. For example, inserting an intrauterine contraceptive device (IUD) in someone with untreated gonorrhoea is categorised as UKMEC 4 because it poses an unacceptable risk; however, someone who contracts and is successfully treated for gonorrhoea can continue to use an IUD that is already in place because it is generally safe (categorised as UKMEC 2).

Table 20.2 Definition of United Kingdom Medical Eligibility Criteria (UKMEC) categories

[NB1]

UKMEC category	Definition
UKMEC 1	A condition for which there is no restriction for the use of the method
UKMEC 2	A condition for which the advantages of using the method generally outweigh the theoretical or proven risks
UKMEC 3	A condition for which the theoretical or proven risks usually outweigh the advantages of using the method. The provision of a method requires expert clinical judgment and/or referral to a specialist contraceptive provider, since use of the method is not usually recommended unless other more appropriate methods are not available or not acceptable
UKMEC 4	A condition that represents an unacceptable health risk if the method is used

NB1: For full details of UKMEC categories of each contraceptive method for specific conditions, see the Faculty of Sexual and Reproductive Healthcare website.

Reproduced with permission from: The Faculty of Sexual and Reproductive Healthcare (FSRH). UK medical eligibility criteria (UKMEC) for contraceptive use. London: FSRH; 2016 (Amended 2019).

Drug interactions with hormonal contraceptives

Drug interactions with hormonal contraceptives

Overview of drug interactions with hormonal contraceptives

Overview of drug interactions with hormonal contraceptives

Drug interactions with hormonal contraceptives can result in decreased effectiveness of the contraceptive. Hormonal contraceptives can also affect the metabolism of some drugs, resulting in either a decreased effect of the drug or risk of toxicity. Check for drug interactions (including with over-the-counter and complementary medicines) when starting a hormonal contraceptive or any new drug.

For detailed information, see the Faculty of Sexual and Reproductive Healthcare guidance Drug Interactions with Hormonal Contraception.

Drugs that affect hormonal contraceptives

Drugs that affect hormonal contraceptives

Most significant drug interactions with hormonal contraceptives are due to induction of cytochrome P450 liver enzymes. Enzyme-inducing drugs increase the metabolism of both estrogens and progestogens, and decrease effectiveness of all hormonal contraceptives other than levonorgestrel-releasing intrauterine contraceptive devices (IUDs) and depot medroxyprogesterone. Copper IUDs (which are nonhormonal contraceptives) are also unaffected by enzyme-inducing drugs.

Levonorgestrel-releasing or copper IUDs and depot medroxyprogesterone are effective in individuals taking enzyme-inducing drugs.

Enzyme-inducing drugs that decrease the effectiveness of hormonal contraceptives include:

- the **antiepileptics** carbamazepine, oxcarbazepine, perampanel (at doses of more than 8 mg daily), phenobarbital (phenobarbitone), phenytoin, primidone, rufinamide and topiramate (at any dose)
- some drugs used to treat viral infections such as HIV, viral hepatitis and coronavirus (COVID-19)—see the University of Liverpool (UK) Drug-Drug Interaction Resource
- the **antibiotics** rifampicin and rifabutin

- some **complementary medicines** (eg St John's wort)
- other drugs (eg aprepitant, modafinil, bosentan).

The only antibiotics that interact with hormonal contraceptives are those that induce liver enzymes (ie rifampicin and rifabutin).

Table 20.3 summarises the reliability of contraception for individuals taking drugs that induce liver enzymes and the recommended actions and alternatives.

Table 20.3 Contraception in individuals taking drugs that induce liver enzymes

Contraceptive method	Recommended action [NB1]
combined oral contraceptive (COC)	use alternative method if possible [NB2] if a COC is used, advise **all** of the following: • increase the daily dose of ethinylestradiol to at least 50 micrograms (ie use two tablets of a COC containing 30 micrograms of ethinylestradiol, or one COC containing 30 micrograms plus one containing 20 micrograms of ethinylestradiol) [NB3] • use the active pills continuously (no hormone-free interval), or for 9 to 12 consecutive weeks followed by a shortened (4-day) hormone-free interval (see Tailored regimens) • consider using a barrier method (eg condoms) as well as the COC, because contraceptive failure is still possible
vaginal ring	use alternative method [NB2]
progestogen-only oral contraceptive	use alternative method [NB2]
etonogestrel implant	use alternative method [NB2]
oral emergency contraception	use a copper IUD
(levonorgestrel or ulipristal)	if a copper IUD is declined or unsuitable, use a double dose of levonorgestrel emergency contraception [NB4]
levonorgestrel-releasing or copper IUD	no action required (effective)
depot medroxyprogesterone	no action required (effective)

IUD = intrauterine contraceptive device

NB1: The effectiveness of contraceptives may be reduced during therapy with, and for at least 4 weeks after stopping, enzyme-inducing drugs; any recommended actions should be continued for this entire duration.

NB2: In individuals taking enzyme-inducing drugs, effective contraception is provided by levonorgestrel-releasing or copper IUDs, and depot medroxyprogesterone.

NB3: Do not use a single combined hormonal pill containing 50 micrograms of ethinylestradiol for individuals taking drugs that induce liver enzymes because it does not contain sufficient progestogen.

NB4: A double dose of levonorgestrel (3 mg, ie 2 × 1.5 mg tablets) can be used; the effectiveness in this situation is unknown and this dose is not approved by the Australian Therapeutic Goods Administration (TGA). A double dose of ulipristal is not advised.

Although **griseofulvin** does not induce cytochrome P450 liver enzymes, the effectiveness of hormonal contraceptives may be reduced by concurrent use. The recommended actions in Table 20.3 apply while taking, and for at least 28 days after stopping, griseofulvin.

Efficacy of combined hormonal contraceptives, all progestogen-only contraceptive pills (POPs) and the etonogestrel implant may be reduced in individuals taking **lamotrigine**; some studies have shown a small reduction in plasma levonorgestrel concentrations and an increase in follicle stimulating hormone (FSH) and luteinising hormone (LH) concentrations. The clinical significance is not known but additional reliable use of condoms is advisable for patients using lamotrigine and combined hormonal contraception, progestogen-only pills or the etonogestrel implant. Contraceptive effectiveness of depot medroxyprogesterone acetate and levonorgestrel-releasing-IUDs is not expected to be affected by lamotrigine.

Drugs affected by hormonal contraceptives

Drugs affected by hormonal contraceptives

The plasma concentration of some drugs can be affected by hormonal contraceptives; monitoring of drug levels or effects may be required. For detailed information, see the Faculty of Sexual and Reproductive Healthcare guidance *Drug Interactions with Hormonal Contraception*.

Effects of hormonal contraception on lamotrigine

Effects of hormonal contraception on lamotrigine

Combined hormonal contraceptives increase the metabolism of lamotrigine. This can result in significantly lower serum lamotrigine concentrations (reduced effect) while taking active (hormone) pills, and may result in increased concentrations (risk of toxicity) during the hormone-free interval. If a combined hormonal contraceptive is the most suitable option for a patient, continuous use (use without a hormone-free interval) of a combined oral contraceptive pill or vaginal ring avoids cyclical changes in lamotrigine concentrations. Measure serum lamotrigine concentrations after starting these contraceptives because lamotrigine dosage may need to be increased (possibly up to 2-fold) to maintain efficacy.

Extrapolating from evidence on the desogestrel progestogen-only pill (unavailable in Australia), use of any form of progestogen-only contraception may increase the risk of lamotrigine toxicity. Advise patients taking lamotrigine who start progestogen-only contraception to alert their clinician to any symptoms of toxicity such as dizziness, co-ordination difficulties or double vision.

When starting or stopping hormonal contraception for a patient taking lamotrigine, consult the patient's neurologist or psychiatrist so that any dose adjustments required can be made.

Effectiveness of contraceptive method

Effectiveness of contraceptive method

Effectiveness of a contraceptive method may be paramount if pregnancy would pose a serious health risk (eg in those with cardiac failure, recent breast cancer, some mental health conditions or complex psychosocial situations).

The estimated effectiveness and efficacy of contraceptive methods is listed in Table 20.4. Typical use (effectiveness) and perfect use (efficacy) can vary by population; younger people generally experience higher failure rates (reduced effectiveness), because they have higher background fertility than older people.

Long-acting reversible contraception (LARC) (which includes intrauterine contraceptive devices (IUDs) and the etonogestrel implant) is the most effective reversible method of contraception.

Patient information about the effectiveness of contraceptive methods and benefits of LARCs is available from Family Planning Alliance Australia.

Table 20.4 Estimated effectiveness and efficacy of contraceptive methods

Contraceptive method	Effectiveness with typical use (%)	Efficacy with perfect use (%)
Extremely effective with minimal patient involvement ('set and forget')		

Contraceptive method	Effectiveness with typical use (%)	Efficacy with perfect use (%)
etonogestrel implant	99.95	99.95
levonorgestrel-releasing IUDs	99.7 to 99.9	99.7 to 99.9
copper IUD	99.5	99.5
sterilisation (male and female)	99.5	99.5
Very effective with typical use		
depot medroxyprogesterone	96	99.8
combined oral contraceptive (COC)	93	99.5
vaginal ring	93	99.5
progestogen-only pill	93	99.5
Least effective with typical use		
condoms: external (male)	88	98
diaphragm	82	86
withdrawal	80	96
condoms: internal (female)	79	95
fertility awareness methods	76 to 93	95 to 99.6

IUD = intrauterine contraceptive device

Starting hormonal contraception without delay (Quick Start)

Starting hormonal contraception without delay (Quick Start)

Hormonal contraception is traditionally started at the beginning of the next normal menstrual period (within the first 5 days of the menstrual cycle) to avoid the risk that the individual is already pregnant. It also avoids the need for an additional method of contraception for the first 7 days, because hormonal contraception is immediately effective if started at this time [Note 1].

Quick Start refers to starting a hormonal contraceptive immediately at the time of consultation even if it is later than day 5 of the menstrual cycle, when it may be impossible to exclude an early pregnancy. If following oral emergency contraception, Quick Start can be used immediately after taking levonorgestrel but not until 5 days (120 hours) after taking ulipristal.

Quick Start can be used for all methods of contraception other than:

- levonorgestrel-releasing and copper intrauterine contraceptive devices (IUDs), because early pregnancy must be excluded before starting an IUD. IUDs can cause harm to a continuing pregnancy (including late miscarriage and premature delivery) if the IUD cannot be safely removed
- combined oral contraceptives containing cyproterone, unless pregnancy can be reasonably excluded, because there is a theoretical risk of feminisation of a male fetus.

For information about excluding pregnancy, see Before starting an IUD.

Quick Start can be considered for anyone presenting for hormonal contraception, but is particularly useful if:

- the menstrual cycle is long or irregular
- unintended pregnancy would pose medical or psychological harm (to avoid delay in contraception)
- there may be difficulties accessing health services at a later time (eg for insertion of the etonogestrel implant).

If using the Quick Start approach, ensure the individual is aware that:

- as early pregnancy has not been excluded, a pregnancy test is required 4 weeks after starting the contraceptive (or 3 weeks after starting if no further episodes of unprotected sex occurred in the first week of use) regardless of whether bleeding occurs

- there are no known teratogenic effects from the contraceptive method
- the method will take 7 days to become effective [Note 1] (or 48 hours [3 consecutive tablets] for those progestogen-only pills that contain levonorgestrel or norethisterone).

Note 1: The quadriphasic combined oral contraceptive Qlaira is only immediately effective if started on day 1 of the menstrual cycle. If started on day 2 or later, an additional method of contraception is required for 9 days.

Contraceptive choice by reproductive stage of life

Contraceptive choice by reproductive stage of life

Adolescence and contraception

Adolescence and contraception

Young people are highly fertile and require effective contraception to prevent unintended pregnancy.

Contraception (excluding sterilisation) can be provided without parental consent to adolescents assessed as being able to consent to their own medical treatment [Note 2]. Clinicians should be aware of mandatory reporting requirements in their jurisdiction for young people assessed as being at risk of harm (eg nonconsensual sexual activity, significant age gap or power differential between the young person and the sexual partner).

Provide information about prevention of sexually transmitted infections (STIs) (including dual contraception with condoms and another effective method) and the availability of emergency contraception without the need for a prescription.

Long-acting reversible contraception (LARC) (the etonogestrel implant and intrauterine contraceptive devices [IUDs]) is the first-line option in adolescence. These methods are highly effective, and have high continuation and user satisfaction rates. IUDs can be safely used by young nulliparous individuals.

IUDs can be safely used by young nulliparous individuals.

Depot medroxyprogesterone injection (DMPA) is useful as a discreet method of contraception. It is generally safe to use (UKMEC 2) in adolescence, but is usually not first line; it may theoretically limit peak bone mineral density, although this has not been proven in clinical trials.

Combined hormonal contraception (combined oral contraceptives [COCs] and the contraceptive vaginal ring) are sometimes preferred by adolescents because they can be easily stopped and restarted, and allow manipulation of the menstrual cycle with a tailored regimen (eg to avoid unnecessary withdrawal bleeding). They are also useful in the management of acne, dysmenorrhoea and heavy menstrual bleeding, which are common in adolescence. The cost of some formulations of COCs and the vaginal ring may limit their use in adolescence. Combined hormonal contraception requires greater patient involvement than long-acting contraceptives; unintended pregnancy is more likely in those younger than 21 years compared to older users.

Progestogen-only pills (POPs) that contain levonorgestrel or norethisterone are less effective in younger people than LARC, DMPA, combined hormonal contraception, or POPs that contain drospirenone. Younger people have higher background fertility; failure rates for these POPs are higher in those younger than 25 years compared to older people.

Note 2: For more information on consent in children, see the Royal Australian College of General Practitioners (RACGP) website.

Postpartum contraception

Postpartum contraception

Choice of contraception in the first 6 weeks postpartum is limited by the risk of venous thromboembolism and by breastfeeding. For the UKMEC restrictions on postpartum use of hormonal contraception, see the Faculty of Sexual and Reproductive Healthcare website.

Although contraception is not required until 21 days after delivery, an immediate start before leaving hospital eliminates the need for a return visit and can reduce the risk of rapid repeat pregnancy.

The etonogestrel implant can be inserted any time postpartum, including immediately before leaving hospital and during breastfeeding.

A levonorgestrel-releasing or copper intrauterine contraceptive device (IUD) can be inserted immediately postpartum (within 48 hours), including after a caesarean delivery and while breastfeeding. IUD insertion between 48 hours and 4 weeks postpartum should only be considered in exceptional circumstances by a specialist or experienced provider (UKMEC 3) because there is a higher risk of expulsion, malposition or perforation.

IUD insertion is considered safe from 4 weeks postpartum (UKMEC 1), but there is a higher risk of perforation in postpartum individuals, particularly those who are breastfeeding. Evidence is insufficient to determine whether a caesarean section is associated with an increased risk of perforation. The risk of perforation is increased up to 36 weeks postpartum. Individuals who are breastfeeding have a higher relative risk of perforation (six-fold increase), but the absolute risk of perforation remains low (approximately 1 in 100 people).

Depot medroxyprogesterone injection is safe to use (UKMEC 2) immediately postpartum and during breastfeeding. It can be a useful option for those awaiting IUD insertion after delivery.

Progestogen-only pills (POPs) are commonly prescribed for individuals who are breastfeeding because they do not increase the risk of VTE (unlike combined hormonal contraception). POPs that contain levonorgestrel or norethisterone have to be taken within a narrow 3-hour window each day (a maximum interval of 27 hours between pills); this timing can be challenging at this busy stage of life. POPs containing drospirenone may be easier to use because the maximum interval between pills is 48 hours (the same duration as for combined oral contraceptive pills). All POPs can be started immediately after delivery.

Combined hormonal contraception (COC or contraceptive vaginal ring) can generally be used from 6 weeks postpartum, even if breastfeeding. It does not adversely affect breastmilk or neonatal growth when used from 6 weeks.

Combined hormonal contraception can be used from 6 weeks postpartum, even if breastfeeding.

Condoms can be started at any time postpartum, but use of a diaphragm is not recommended until 6 weeks postpartum.

Lactational amenorrhoea is 98% effective if all the criteria for use are met (see here for more information). However, an additional method of contraception is generally recommended if possible.

Contraception for females aged 40 to 49 years

Contraception for females aged 40 to 49 years

Although any form of contraception can potentially be used in females aged 40 years or older, there are some additional age-related considerations. These include an increased likelihood of comorbidities, which may limit choices, and of conditions that may benefit from the noncontraceptive effects of hormonal contraceptives.

The 52 mg levonorgestrel-releasing IUD can be useful to manage heavy menstrual bleeding in perimenopausal individuals.

Combined hormonal contraception can be useful to manage heavy menstrual bleeding and menopausal symptoms, and to prevent loss of bone mineral density. The risk of cardiovascular disease and venous thromboembolism (VTE) increases with age, which may limit their use; see Contraception and venous thromboembolism.

Although depot medroxyprogesterone injection can be used (UKMEC 2) in individuals aged 45 to 49 years, it is generally not started in this age group. It is not recommended for individuals older than 45 years who have cardiovascular risk factors because it has an adverse effect on lipids. It is also associated with a loss of bone mineral density, which may not be regained before the drop in bone mineral density associated with menopause. For individuals older than 45 years continuing to use depot medroxyprogesterone, assess for other osteoporosis risk factors on an annual basis; a dual energy X-ray absorptiometry (DXA) scan can be considered on a case-by-case basis.

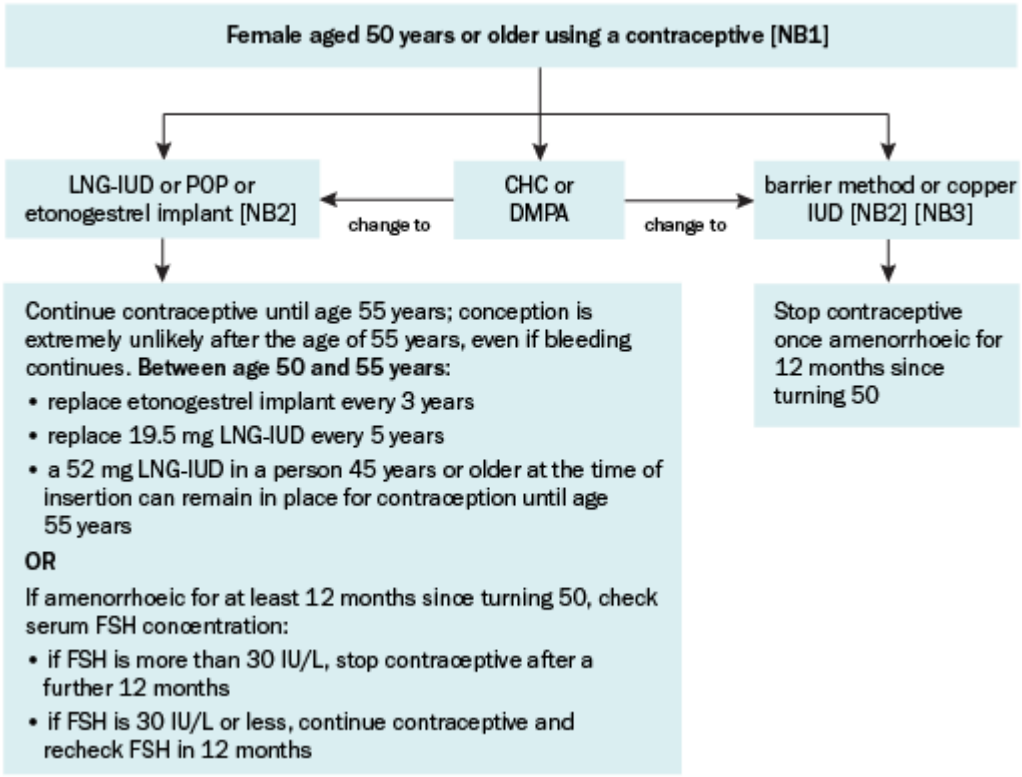
Contraception for females aged 50 years and older

Contraception for females aged 50 years and older
Overview of contraception for females aged 50 years and older

Choice of contraceptive should be reviewed when a female reaches the age of 50 years, and at menopause. An overview of contraception in females aged 50 years or older is given in Figure 20.1.

Figure 20.1 Contraception for females aged 50 years and older (Figure 20.1)

Printable Figure



CHC = combined hormonal contraception (combined oral contraceptive [COC] or contraceptive vaginal ring); DMPA = depot medroxyprogesterone; FSH = follicle stimulating hormone; IUD = intrauterine contraceptive device; LNG-IUD = levonorgestrel-releasing IUD; MHT = menopausal hormone therapy; POP = progestogen-only pill

NB1: Investigate any bleeding suspicious of underlying pathology; risks of endometrial cancer and other serious pathology increase with age.

NB2: Contraceptives suitable for people aged 50years or older can be combined with systemic MHT. The 52mg LNG-IUD can be combined with estrogen-only MHT. Other contraceptive methods cannot be

combined with estrogen-only MHT for endometrial protection because evidence is lacking for a suppressive effect on estrogen-driven endometrial hyperplasia. Although data are limited on concurrent use for contraception, the etonogestrel implant, POP and copper IUD can be combined with cyclical combined MHT. The efficacy of barrier methods is not affected by the use of MHT.

NB3: Any copper IUD approved for use in Australia inserted in someone aged 40 years or older can be left in place until menopause is diagnosed. Heavy bleeding associated with the copper IUD may limit its use in some perimenopausal patients.

Modified with permission from: Contraception for users over 40 years: health practitioner FAQs Fact sheet. Melbourne: Family Planning Victoria (FPV); 2020.
Reviewing hormonal contraception at age 50 years

Once a female turns 50 years old, recommend switching from combined hormonal contraception or depot medroxyprogesterone, because the risks of these methods generally outweigh the benefits. If benefits such as amenorrhoea are desired, continuation of depot medroxyprogesterone can be considered on a case-by-case basis provided there are no risk factors for cardiovascular disease or osteoporosis.

Suitable contraceptive options for females aged between 50 and 55 years are the etonogestrel implant, a levonorgestrel-releasing IUD, copper IUD, progestogen-only pills and barrier methods.

Because fertility is reduced at this age, strict timing of progestogen-only pills (POPs) that contain levonorgestrel or norethisterone may be less important than in younger people. Reduced fertility may also mean that:

- less effective contraceptive methods (eg condoms, the diaphragm) are also acceptable.
- extended use of some IUDs is considered safe; it also avoids the risks associated with device removal and replacement.

If concurrent systemic menopausal hormone therapy (MHT) is required, see Figure 20.1 for advice on suitable combinations of MHT and contraceptives.

Reviewing hormonal contraception at perimenopause

Onset of menopause can be difficult to determine in individuals using hormonal methods of contraception. All hormonal methods can induce amenorrhoea, and withdrawal bleeds will continue while using combined hormonal contraception, regardless of menopausal status.

Evidence is lacking to guide decisions about when to stop hormonal contraception in females younger than 50 years in whom menopause is suspected; the decision to stop contraception should be made jointly with the individual.

Conception after the age of 55 years is extremely unlikely; individuals using a levonorgestrel-releasing IUD, etonogestrel implant or progestogen-only pill should generally stop at 55 years.

Alternatively, a single serum follicle stimulating hormone (FSH) concentration can be measured once the individual has been amenorrhoeic for at least 12 months since turning 50. If the FSH is more than 30 IU/L, stop contraception after a further 12 months. If the serum FSH concentration is 30 IU/L or less the test can be repeated 12 months later. At the time of writing, measuring serum anti-Mullerian hormone (AMH) is not useful for predicting the need for contraception.

Contraception after abortion

Contraception after abortion

Contraception after surgical abortion

Contraception after surgical abortion

Sexual intercourse should be avoided for 1 to 2 weeks after surgical abortion to minimise risk of infection.

Provide advice about the range of contraceptive options to support informed decision-making.

All methods of contraception can be started immediately after a first- or second-trimester surgical abortion; this includes immediate insertion of a levonorgestrel-releasing or copper intrauterine contraceptive device (IUD).

For third-trimester surgical abortions, the medical eligibility criteria for contraception use are the same as for postpartum; see the Faculty of Sexual and Reproductive Healthcare UK Medical Eligibility Criteria.

Hormonal methods of contraception are immediately effective if started within 5 days of the procedure, and take 7 days to work if started later [Note 3].

Note 3: The quadriphasic combined oral contraceptive Qlaira takes 9 days to become effective.

Contraception after medical abortion

Contraception after medical abortion

Sexual intercourse should be avoided for 1 week after medical abortion to minimise risk of infection.

Provide advice about the range of contraceptive options to support informed decision-making.

Although progestogen-containing contraceptives can theoretically compete with mifepristone at the receptor site, the etonogestrel implant has not been shown to reduce the effectiveness of mifepristone. It can be inserted on the day mifepristone and misoprostol is prescribed or at any time after the abortion.

Depot medroxyprogesterone (DMPA) injection can be given any time after the abortion. Although evidence to confirm that it does not reduce efficacy of mifepristone is insufficient, DMPA can be given on the day mifepristone and misoprostol is prescribed, particularly if there is a concern the individual may be unable to return for an injection.

The combined oral contraceptive (COC) (starting with an active pill) or progestogen-only pill can be started on the day after mifepristone is taken.

The contraceptive vaginal ring can be inserted once the heaviest bleeding of a medical abortion is complete.

A levonorgestrel-releasing or copper intrauterine contraceptive device (IUD) can be inserted at a follow-up visit 2 to 3 weeks after a medical abortion, provided there is no evidence of ongoing viable pregnancy or infection. Advise another method of contraception or abstinence until the IUD is inserted.

Hormonal methods of contraception are immediately effective if started within 5 days of taking mifepristone, and take 7 days to work if started later [Note 4].

Note 4: The quadriphasic combined oral contraceptive Qlaira takes 9 days to become effective.

Contraception for trans individuals

Contraception for trans individuals

Trans and gender diverse (trans) individuals have a different gender identity from that originally presumed or assigned at birth. As for all individuals wanting to prevent pregnancy, contraceptive choice is influenced by multiple factors (see Overview of factors affecting contraceptive choice). Gender identity does not restrict choice of contraceptive method, but additional factors may need consideration in trans individuals.

For **trans individuals presumed female at birth (ie trans men and some nonbinary individuals)**:

- Although testosterone can cause amenorrhoea, it does not provide adequate contraception, and is contraindicated in pregnancy due to its teratogenic effect on a female fetus.
- Estrogen-containing contraceptives are not recommended if testosterone therapy is being used; progestogen-only methods can be used.
- A desire for amenorrhoea may influence choice of contraceptive method. A levonorgestrel-releasing intrauterine contraceptive device (LNG-IUD) or depot medroxyprogesterone can be useful choices; for individuals not using testosterone therapy, continuous use of combined hormonal contraception can effectively reduce blood loss.
- Body dysphoria in relation to genital procedures can impact on the procedure for inserting intrauterine contraception and cause distress; consider using distraction techniques or sedation.

For **trans individuals presumed male at birth (ie trans women and some nonbinary individuals)**:

- Although estrogen therapy impairs spermatogenesis, it cannot be relied on for contraception.
- For those who have not undergone orchiectomy, contraceptive options are limited to vasectomy and condoms.

See also Trans and gender diverse health for other aspects of healthcare.

Contraception in individuals with acne

Contraception in individuals with acne

All combined oral contraceptives (COCs) increase sex hormone–binding globulin and lower serum androgen concentrations, which may reduce acne. Evidence is lacking for an effect of the contraceptive vaginal ring on acne, but it is likely to have a similar effect to COCs.

Some COCs have an indication for acne; however, this does not indicate superiority to those containing other hormone combinations (in which trials to examine effect on acne have not been undertaken).

Although COCs containing an antiandrogenic progestogen (eg dienogest, drospirenone, cyproterone) or a less androgenic progestogen than levonorgestrel (eg desogestrel, gestodene, norethisterone) might theoretically be most beneficial, there is insufficient evidence to indicate superiority of one COC formulation over another for acne. COCs containing cyproterone, desogestrel, drospirenone or gestodene may be associated with a slightly higher risk of venous thromboembolism (VTE) compared to pills containing levonorgestrel or norethisterone (see Table 20.5).

Contraception in individuals with depression

Contraception in individuals with depression

The effect of hormonal contraceptives on depression has not been determined in clinical trials. While an association between a first prescription of an antidepressant and hormonal contraception has been found (particularly in adolescents), a causal link has not been proven. Advise users of hormonal contraception to report new or worsening mood-related symptoms.

Combined oral contraceptives (COCs) are of benefit in premenstrual dysphoric disorder, but data on their effect on other mood symptoms (including premenstrual syndrome) is limited; tailored regimens that avoid or minimise hormone-free intervals may help reduce premenstrual mood symptoms.

Contraception in obesity

Contraception in obesity

Overview of contraception in obesity

Overview of contraception in obesity

Effective contraception is important for individuals with obesity because unplanned pregnancy is associated with significant health risks. Challenges include:

- increased risk of venous thromboembolism (VTE) with combined hormonal contraception
- malabsorption of oral formulations after bariatric surgery
- potential exacerbation of weight gain by depot medroxyprogesterone
- reduction in bone mineral density by depot medroxyprogesterone, which may compound bone loss due to malabsorption after bariatric surgery
- reduced effectiveness of emergency hormonal contraception.

The etonogestrel implant and levonorgestrel-releasing and copper intrauterine contraceptive devices (IUDs) are effective and safe methods of contraception for individuals with obesity. Depot medroxyprogesterone is a second-line option.

The etonogestrel implant and levonorgestrel-releasing and copper IUDs provide effective contraception in individuals with obesity.

IUDs should ideally be inserted by an experienced practitioner, because visualising the cervix, accessing the uterus and managing a vasovagal episode can be difficult in individuals with obesity.

Safety of hormonal contraceptives in obesity

Safety of hormonal contraceptives in obesity

Use of combined hormonal contraception (combined oral contraceptives [COCs] or the contraceptive vaginal ring) in individuals with a body mass index (BMI) of 30 to 34 kg/m^2 is considered safe (UKMEC 2). Their use in those with a BMI more than 35 kg/m^2 requires expert judgment or referral (UKMEC 3), particularly if they have other cardiovascular risk factors.

Safety concerns for individuals with obesity using combined hormonal contraception are related to the effects of estrogen on cardiovascular risk (including VTE, acute myocardial infarction and stroke). Users of combined hormonal contraception who are obese are at further increased risk of VTE (including a possible higher risk of cerebral venous thrombosis) compared to users who are of normal weight. It is unknown whether obesity increases the risk of ischaemic stroke and myocardial infarction in users of combined hormonal contraception.

Effectiveness of contraceptives in obesity

Effectiveness of contraceptives in obesity

Combined hormonal contraception, progestogen-only pills, levonorgestrel-releasing IUDs (LNG-IUDs) and depot medroxyprogesterone do not require dose adjustment in individuals with obesity.

Early replacement of the etonogestrel implant (after the second year of use) may be considered on a case-by-case basis if regular cycles resume. However, there is no evidence to suggest an increase in pregnancies in the third year of use in individuals with a high BMI.

The effectiveness of oral emergency contraception may be affected by increased weight:

- Levonorgestrel may be less effective if BMI is more than 26 kg/m^2 or weight is more than 70 kg; consider a copper IUD or a double dose of levonorgestrel.
- Ulipristal may be less effective if the BMI is more than 30 kg/m^2 or weight is more than 85 kg; consider a copper IUD (a double dose of ulipristal is not recommended).

Weight gain in individuals using hormonal contraceptives

Weight gain in individuals using hormonal contraceptives

Around 25% of depot medroxyprogesterone users experience weight gain, particularly those younger than 18 years with a BMI of 30 kg/m^2 or more. Early weight gain appears to be a predictor of continued gain.

There is insufficient evidence to determine whether other forms of hormonal contraception cause weight gain.

Contraception after bariatric surgery

Contraception after bariatric surgery

Pregnancy should be avoided for 12 months after bariatric surgery because it may be associated with an increased risk of maternal and child complications.

A nonoral method of contraception should be used, because absorption of oral contraceptives may be reduced after bariatric surgery. An IUD, etonogestrel implant or vaginal ring may be preferred options, because both depot medroxyprogesterone and bariatric surgery are associated with a loss of bone mineral density.

Contraception and venous thromboembolism

Contraception and venous thromboembolism

Thromboembolic risk and combined hormonal contraception

Thromboembolic risk and combined hormonal contraception

All combined hormonal contraceptives (combined oral contraceptives [COCs] or the contraceptive vaginal ring) increase the relative risk of venous thromboembolism (VTE), but the absolute risk is still very low. The risk is highest in the first year of use, but remains above that of nonusers for the duration of use. Combined hormonal contraceptives containing cyproterone, desogestrel, drospirenone, gestodene or etonogestrel may be associated with a slightly higher risk of VTE than combined hormonal contraceptives containing levonorgestrel or norethisterone; see Table 20.5.

All users of combined hormonal contraception should be informed of the signs and symptoms of VTE.

Table 20.5 Risk of developing venous thromboembolism with combined hormonal contraception

Contraceptive	Estimated annual VTE incidence per year of use
females of reproductive age who are not using a combined hormonal contraceptive and are not pregnant	2 out of 10 000 females
combined hormonal contraceptive containing levonorgestrel or norethisterone	5 to 7 out of 10 000 females
combined hormonal contraceptive containing etonogestrel	6 to 12 out of 10 000 females
combined hormonal contraceptive containing drospirenone, gestodene or desogestrel [NB1]	9 to 12 out of 10 000 females
combined hormonal contraceptive containing dienogest or nomegestrol	not known

COCs = combined oral contraceptives; VTE = venous thromboembolism

NB1: COCs containing cyproterone are estimated to have a similar risk of VTE to those containing drospirenone, gestodene or desogestrel.

Contraceptive	Estimated annual VTE incidence per year of use

Adapted with permission from: Benefits of combined hormonal contraceptives (CHCs) continue to outweigh risks—CHMP endorses PRAC recommendation: European Medicines Agency; 2013 cited 13 September 2019.

Use of combined hormonal contraception is contraindicated (UKMEC 4) in individuals with the following risk factors for VTE:

- current or past history of VTE
- known thrombogenic mutation (see Thrombophilias and VTE risk in contraception)
- antiphospholipid antibodies
- major surgery with prolonged immobilisation
- between 0 to 3 weeks postpartum with additional risk factors (such as caesarean section or postpartum haemorrhage).

Use of combined hormonal contraception requires expert clinical judgment or referral (UKMEC 3) because of VTE risk in individuals:

- with a body mass index (BMI) more than 35 kg/m^2 (see Contraception in obesity)
- with a first-degree relative with a VTE (provoked or unprovoked) under the age of 45 years, regardless of thrombophilia screening results
- who are between 0 to 3 weeks postpartum, and do not have additional risk factors (and are not breastfeeding [Note 5])
- who are between 3 to 6 weeks postpartum, and **do** have additional VTE risk factors (see list of contraindications above) (and are not breastfeeding [Note 5]).

Note 5: Use of combined hormonal contraception before 6 weeks is contraindicated (UKMEC 4) if breastfeeding to limit possible (unproven) impact on neonatal growth])

Thrombophilias and VTE risk in contraception

Thrombophilias and VTE risk in contraception

Do not routinely screen for thrombophilias before starting combined hormonal contraception; screening is not cost-effective or clinically helpful.

Use of combined hormonal contraception is not recommended without expert clinical judgment or referral if there is a family history of VTE in a first-degree relative before age 45 years (provoked or unprovoked). Although screening for thrombophilias can be considered in this situation, a negative screen may not exclude all thrombogenic mutations.

Thromboembolic risk and depot medroxyprogesterone

Thromboembolic risk and depot medroxyprogesterone

Depot medroxyprogesterone is not associated with a clinically significant risk of VTE. Despite a small increase in VTE risk if started in the first week postpartum, it is considered safe to use (UKMEC 2) immediately postpartum.

Other progestogen-only contraceptives are not associated with an increased risk of VTE.

Contraception in individuals with migraine

Contraception in individuals with migraine

Stroke risk in individuals with migraine

Stroke risk in individuals with migraine

Individuals with migraine have an increased risk of stroke compared to those who are migraine-free. The association is much stronger for those who experience aura (reversible focal neurological symptoms) than for those who do not.

Contraception in individuals with migraine with aura

Contraception in individuals with migraine with aura

Combined hormonal contraception is contraindicated in individuals with migraine with aura because it further increases the risk of stroke (UKMEC 4).

If it has been 5 or more years since the individual last experienced a migraine with aura, use of combined hormonal contraception requires expert clinical judgment or referral (UKMEC 3).

Progestogen-only methods of contraception are safe to use (UKMEC 2) for individuals with a current or past history of migraine with aura.

Contraception in individuals with migraine without aura

Contraception in individuals with migraine without aura

Use of combined hormonal contraception is generally safe (UKMEC 2) in individuals with migraine without aura, although evidence is insufficient to rule out a small increase in stroke risk. If users of combined hormonal contraception develop migraine without aura for the first time, ongoing use requires expert clinical judgment or referral (UKMEC 3).

Progestogen-only methods of contraception are safe to use (UKMEC 2) for individuals with a current or past history of migraine without aura.

Contraception in people who smoke tobacco or use nicotine vaping products

Contraception in people who smoke tobacco or use nicotine vaping products

Tobacco smoking is a risk factor for cardiovascular disease, and increases cancer risk, including that of breast and cervical cancer. In the absence of long-term evidence, vaping with nicotine is currently considered to confer the same risks as tobacco smoking in relation to contraceptive choice.

Combined hormonal contraception is contraindicated (UKMEC 4) in individuals 35 years or older who smoke 15 or more cigarettes per day; see also Contraindications and precautions for combined hormonal contraception. Because it is not possible to determine equivalence of exposure between vaping and tobacco smoking, any nicotine vaping in a person aged 35 years or older is a contraindication to the use of combined hormonal contraception according to Australian consensus.

Use of depot medroxyprogesterone requires expert judgment or referral (UKMEC 3) in people who smoke tobacco and have additional risk factors for cardiovascular disease (eg obesity, diabetes, age older than 45 years); all other contraceptives except for combined hormonal methods are considered safe. Australian consensus indicates the same considerations apply to people who vape nicotine.

People who smoke tobacco or vape nicotine and do not have additional risk factors for cardiovascular disease can use any method of contraception, with the exception of combined hormonal contraception in those 35 years or older.

Contraception and cancer risks

Contraception and cancer risks

Overview of contraception and cancer risks

Overview of contraception and cancer risks

For individuals with a past or current history of cancer (or who are at high cancer risk), weigh up the risks of contraception against those of pregnancy. While hormonal contraception can be safely used in individuals with most cancers, use in some situations needs special consideration.

Breast cancer and contraception

Breast cancer and contraception

Users of combined hormonal contraception have a very small increase in the risk of breast cancer, equating to around 1.3 additional cancers per 10 000 users per year (0.2 additional cancers per 10 000 users in those younger than 35 years).

All hormonal contraception (except for oral emergency contraception) is contraindicated (UKMEC 4) in individuals with current breast cancer. Expert clinical judgment or referral is advised (UKMEC 3) for individuals with past breast cancer who are considering any form of hormonal contraception (other than oral emergency contraception).

A family history of breast cancer is not a contraindication to the use of hormonal contraception; however, expert clinical judgment or referral is advised (UKMEC 3) before use of combined hormonal contraception in those with a known gene mutation that increases the risk of breast cancer [Note 6].

Note 6: For more information on mutation carriers and familial breast cancer risk, see the eviQ website.

Cervical cancer and contraception

Cervical cancer and contraception

The risk of cervical cancer is decreased in users of intrauterine contraceptive devices (IUDs).

Users of combined hormonal contraception (and possibly depot medroxyprogesterone) in Australia have a small increase in the risk of cervical cancer. This risk is likely to have little impact because of cervical cancer screening and human papilloma virus (HPV) immunisation programs. Encourage screening and vaccination before starting combined hormonal contraception.

All methods of contraception can be used in individuals diagnosed with high-risk HPV or cervical intraepithelial neoplasia.

All methods of contraception except for IUDs can be used in individuals with cervical cancer. Expert clinical judgment or referral is advised (UKMEC 3) for those who have had a radical trachelectomy (removal of the cervix with surrounding tissue and upper vagina). If already in place, an IUD can remain in place while awaiting treatment for cervical cancer.

If an individual with an IUD already in place requires a large loop excision of the transformation zone (LLETZ) procedure to investigate and treat cervical abnormalities detected on screening, the IUD must be removed before the procedure. The decision to insert an IUD in an individual awaiting assessment for a LLETZ procedure depends on alternative contraceptive options and the likely waiting time for the procedure.

Endometrial cancer and contraception

Endometrial cancer and contraception

The risk of endometrial cancer is decreased in users of combined hormonal methods of contraception and IUDs.

All methods of contraception except for IUDs can be used in individuals awaiting treatment for endometrial cancer. If already in place, an IUD can remain in place while awaiting treatment for endometrial cancer. Levonorgestrel-releasing IUDs are sometimes used to treat low-grade endometrial cancer in the specialist setting for individuals wishing to preserve fertility.

Ovarian cancer and contraception

Ovarian cancer and contraception

The risk of ovarian cancer is decreased in users of combined hormonal contraception and IUDs.

All methods of contraception can be safely used in individuals with current or past ovarian cancer.

Liver cancer and contraception

Liver cancer and contraception

Combined hormonal contraception is contraindicated in individuals with liver cancer (UKMEC 4). The risks outweigh the benefits for all other hormonal methods of contraception, except for oral emergency contraception, which is safe to use.

Contraception in individuals with a developmental disability

Contraception in individuals with a developmental disability

Individuals living with developmental disability who require contraception need to be assessed for their capacity to consent to treatment. See Consent, capacity and decision making for people with developmental disability.

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Definition of male androgen deficiency

Definition of male androgen deficiency

This topic covers management of androgen deficiency in cis men; for advice on gender-affirming hormone therapy and gender-inclusive primary healthcare, see resources for trans and gender diverse health care. For information on androgen deficiency in childhood, see Delayed puberty in males.

Male androgen deficiency is defined as impaired testosterone production (due to proven dysfunction in the hypothalamic–pituitary–testicular [HPT] axis) that causes symptoms or effects on target organs.

Male hypogonadism is male androgen deficiency accompanied by impaired fertility; it may be:

- **hypergonadotrophic**—caused by primary (testicular) disorders that reduce testosterone production and spermatogenesis; these, in turn, reduce negative feedback on gonadotrophin (luteinising hormone [LH] and follicle stimulating hormone [FSH]) production, leading to increased gonadotrophin concentrations
- **hypogonadotrophic**—caused by a central (hypothalamic or pituitary) disorder that reduces production of gonadotrophins, diminishing stimuli to the testis to produce hormones and sperm.

For treatment of infertility in male hypogonadism, see Gonadotrophin therapy for male infertility.

Causes of male androgen deficiency

Causes of male androgen deficiency

Primary male androgen deficiency causes symptoms or signs of androgen deficiency, low serum testosterone concentration and elevated serum luteinising hormone (LH) concentration. It results from testicular disorders, including:

- Klinefelter syndrome [Note 1]
- cryptorchidism
- orchidectomy
- orchitis
- cytotoxic or radiation damage to the testes
- testicular torsion or trauma
- androgen synthesis inhibitors.

Central androgen deficiency causes symptoms or signs of androgen deficiency and low serum testosterone and LH concentrations. It results from hypothalamic or pituitary disorders, including hyperprolactinaemia.

- pituitary tumours
- pituitary surgery or radiotherapy
- haemochromatosis, which can cause iron deposition in the hypothalamus and pituitary
- hypophysitis
- idiopathic hypogonadotrophic hypogonadism (including Kallmann syndrome, notable for reduced or absent sense of smell [Note 2]
- gonadotrophin-releasing hormone (GnRH) analogues.

Conditions to be distinguished from central androgen deficiency include:

- exogenous synthetic androgen use

- recent acute illness and convalescence
- functionally low testosterone concentrations.

Use of **exogenous synthetic androgens** may result in a biochemical picture that is similar to central androgen deficiency, but without the expected clinical signs of androgen deficiency; see History and examination.

Recent acute illness and convalescence can cause temporary hypothalamic–pituitary–testicular axis suppression.

Also consider the possibility of functionally low serum testosterone concentration , in which total serum testosterone concentration is usually only mildly reduced in men with comorbidities.

Note 1: For information on Klinefelter syndrome, see the US National Library of Medicine Medline Plus website.

Note 2: For information on Kallmann syndrome, see the US National Library of Medicine Medline Plus website

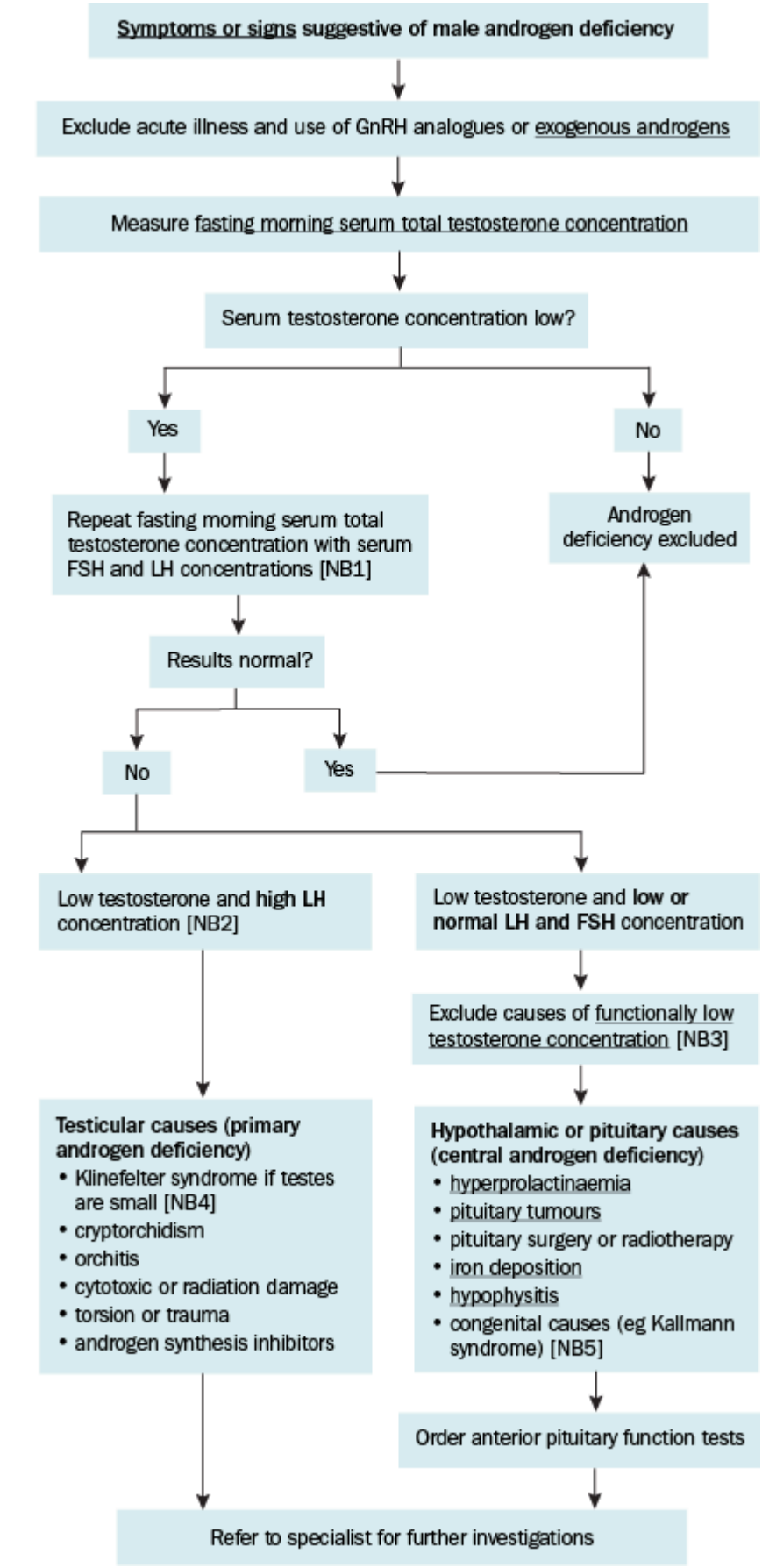
Overview of diagnosis of male androgen deficiency

Overview of diagnosis of male androgen deficiency

Figure 20.14 outlines an approach to diagnosis in suspected androgen deficiency. The aims are to:

- determine whether criteria for androgen deficiency are met
- exclude differential diagnoses
- undertake initial investigations to seek the cause of androgen deficiency (if feasible) before referral.

Figure 20.14 Approach to diagnosis in suspected male androgen deficiency



FSH = follicle stimulating hormone; GnRH = gonadotrophin-releasing hormone; LH = luteinising hormone

NB1: Serum FSH concentration may be easier to interpret than LH, as LH is pulsatile. Serum FSH concentration is also part of assessment for male infertility, which can accompany some causes of androgen deficiency.

NB2: Low testosterone and slightly elevated LH concentrations may be due to normal ageing; see Interpreting serum testosterone concentrations..

NB3: Mildly low testosterone and normal LH concentrations may be due to comorbidities such as obesity, diabetes, depression, or use of opioids, high-dose corticosteroids, alcohol or marijuana; see Interpreting serum testosterone concentrations.

NB4: For information on Klinefelter syndrome, see the US National Library of Medicine Medline Plus website.

NB5: For information on Kallmann syndrome, see the US National Library of Medicine Medline Plus website.

History and examination in male androgen deficiency

History and examination in male androgen deficiency

Androgen deficiency should not be diagnosed unless symptoms and signs are found on history and examination. Many symptoms of androgen deficiency are nonspecific.

Symptoms and signs most likely to indicate androgen deficiency include reduced libido, decreased spontaneous erections, hot flushes, reduced facial hair growth, breast discomfort or gynaecomastia, loss of axillary and pubic hair, small testes (especially volume under 5 mL, assessed using an orchidometer) and low bone mass (particularly low Z-scores). Very small testes are a feature of Klinefelter syndrome [Note 3], which is often missed unless a testicular examination is performed.

Examine men with suspected androgen deficiency for small testes.

Less specific symptoms and signs of androgen deficiency include decreased energy, motivation, concentration, memory or work performance; low mood; disturbed sleep or increased sleepiness; reduced muscle bulk and strength; increased body fat or body mass index; and mild anaemia. Many of these features may be seen with different diagnoses associated with low serum testosterone, such as:

- functionally low serum testosterone concentration
- acute illness.

Rather than typical signs of androgen deficiency (although testicular shrinkage is a feature), use of exogenous androgenic steroids may cause truncal acne and marked muscular development. Ask directly about the use of exogenous synthetic androgens (including unregulated supplements, which may contain unrecognised ingredients).

Ask directly about the use of exogenous androgens, including the use of unregulated supplements.

Note 3: For information on Klinefelter syndrome, see the US National Library of Medicine Medline Plus website.

Interpreting serum testosterone concentrations in diagnosis of male androgen deficiency

Interpreting serum testosterone concentrations in diagnosis of male androgen deficiency

A low serum testosterone concentration must be interpreted in the context of the man's clinical features. For a diagnosis, the following **criteria for diagnosing male androgen deficiency** must all be met:

- symptoms or signs are consistent with male androgen deficiency
- unequivocally low fasting early morning total serum testosterone concentration, confirmed by repeat measurement on a different day

- hypothalamic–pituitary–testicular (HPT) axis dysfunction confirmed.

Serum testosterone concentrations have a wide diurnal variation and are highest in the morning. Samples must be taken between 8 am and 10 am [Note 4], after overnight fasting and confirmed by a repeat measurement on a different day.
Low serum testosterone concentration must be confirmed by repeating the measurement.

Systemic illness temporarily lowers testosterone concentrations and can confound assessment of symptoms. Testosterone should not be measured during an acute illness or convalescence.

Do not measure serum testosterone concentration during an acute illness or convalescence.

Reference ranges for total serum testosterone concentration vary because of factors such as assay method and age. Published ranges relate to mass spectrometry but at the time of writing most laboratories in Australia use immunoassays, so in practice, local reference ranges are used [Note 5].

Some conditions, such as obesity, diabetes and depression, and use of opioids or glucocorticoids, cause a mild reduction in total serum testosterone concentration that does not amount to androgen deficiency, and is generally managed by treating the underlying condition. This finding is referred to as **functionally low total serum testosterone concentration**. Serum gonadotrophin (luteinising hormone [LH] and follicle stimulating hormone [FSH]) concentrations are usually normal; this is consistent with mild functional central suppression of the HPT axis. The underlying conditions may also cause:

- confounding symptoms that overlap with those of androgen deficiency (particularly the less specific features) but are not usually a result of the low testosterone concentration
- reduced hepatic synthesis of sex hormone–binding globulin ([SHBG], the main protein that binds testosterone)—particularly in men with obesity, insulin resistance or glucocorticoid use. This can reduce the total serum testosterone concentration without necessarily affecting the amount of unbound (free) testosterone or having a clinical impact.

Some laboratories report **free serum testosterone concentrations** (calculated using the total serum testosterone and SHBG concentrations). Neither calculations nor reference ranges for free serum testosterone are established. A low free serum testosterone concentration (without a low total serum testosterone concentration) does not warrant testosterone therapy because evidence of clinical benefit is lacking.

If there is uncertainty about the interpretation of serum testosterone concentrations, seek specialist advice.

Note 4: For shift workers or sleep-deprived men, measure testosterone shortly after waking.

Note 5: When assayed by mass spectrometry (not immunoassay which is used by most laboratories), the lower limit for total serum testosterone in males aged 21 to 35 years with normal sexual and reproductive function is 10.4 nanomol/L and in healthy males aged 70 to 89 years is 6.4 nanomol/L. Reference ranges using mass spectrometry are less well defined for males aged 35 to 70 years.

Approach to testosterone replacement therapy

Approach to testosterone replacement therapy

Before considering testosterone replacement therapy, perform assessment as outlined in Figure 20.14 to determine whether criteria for a diagnosis of male androgen deficiency are met.

If criteria are not met but functionally low serum testosterone concentration is suspected, consider whether correction of underlying causes is possible. Management should focus initially on lifestyle measures, particularly weight loss where relevant, and treating comorbidities. Australian management guidelines recommend against testosterone therapy for functionally low serum testosterone concentration. The T-Trials [Note 6] enrolled males with functionally low serum testosterone concentrations and at least one of the following problems: decreased libido, difficulty walking, or low vitality. Testosterone treatment modestly

improved sexual function in those with low libido, walking distance in men with difficulty walking, haemoglobin concentration, and lumbar spine bone mineral density, but questions remain about cardiovascular safety, and long-term clinical outcomes.

Consider referral to an endocrinologist for management of functionally low serum testosterone concentration.

If criteria for diagnosing androgen deficiency are met, investigate causes as outlined in Figure 20.14, if feasible, or refer for investigation and management.
The pathological basis of androgen deficiency should be fully investigated before starting testosterone replacement therapy.

Testosterone replacement aims to relieve the symptoms and signs of androgen deficiency. It is not indicated for treatment of low libido or erectile dysfunction in males who are not androgen deficient. The Pharmaceutical Benefits Scheme criteria for prescribing of testosterone for androgen deficiency are stringent; specialist referral is required. Testosterone replacement suppresses spermatogenesis, so referral to a fertility specialist may be required before starting replacement.

Consider referral to discuss fertility options before starting testosterone replacement therapy.

Androgen deficiency may recover if a reversible cause is treated (eg hyperprolactinaemia is corrected with a dopamine agonist). Androgen deficiency caused by an irreversible disorder requires lifelong testosterone replacement therapy.

Testosterone therapy is contraindicated in males with current prostate or breast cancer, those desiring fertility, and elite athletes (because it is a prohibited substance). For males who have had curative treatment for breast or prostate cancer, specialist assessment of harms and benefits of testosterone therapy is required.

Monitoring of testosterone replacement therapy is advised to assess efficacy and detect adverse effects.

Note 6: Snyder PJ, Bhasin S, Cunningham GR, Matsumoto AM, Stephens-Shields AJ, Cauley JA, et al. Effects of testosterone treatment in older men. N Engl J Med 2016;374(7):611-24. [URL]

Testosterone formulations for replacement therapy

Testosterone formulations for replacement therapy

Overview of testosterone formulations

Overview of testosterone formulations

Testosterone replacement therapy for male androgen deficiency can be undertaken with transdermal, injectable or oral testosterone formulations. The choice of formulation is guided by effectiveness, patient preference, convenience and adverse effects.

Transdermal formulations of testosterone may be preferred over intramuscular formulations if the man wishes to avoid injections, has a bleeding disorder or is taking anticoagulants.

Testosterone injections may be more convenient than daily application of transdermal formulations.

Oral testosterone therapy is less effective than other formulations and is rarely used.

Transdermal testosterone replacement therapy

Transdermal testosterone replacement therapy

For transdermal testosterone replacement therapy, use:

1 testosterone 5% cream 2 mL (100 mg) transdermally, in the morning applied to the trunk or proximally on the limbs. Adjust in 1 mL (50 mg) increments according to clinical response and serum testosterone concentration. Maximum dose 4 mL (200 mg) daily *male androgen deficiency, topical therapy*

OR

1 testosterone 1% gel 5 g (50 mg) transdermally, in the morning applied to the trunk or proximally on the limbs. Adjust in 2.5 g (25 mg) increments according to clinical response and serum testosterone concentration. Maximum dose 10 g (100 mg) daily [Note 7]

OR

1 testosterone 2% gel 1 pump (23 mg/1.15 g) transdermally, in the morning applied to trunk or proximally on the limbs. Adjust in 1 pump (23 mg) increments according to clinical response and serum testosterone concentration. Maximum dose 3 pumps (69 mg/3.45 g) daily

OR

2 testosterone patch 5 mg per 24 hours transdermally, at night applied to the trunk or proximally on the limbs for 24 hours. Adjust in 2.5 mg per 24 hours increments according to clinical response and serum testosterone concentration. Maximum dose 7.5 mg per 24 hours.

See Monitoring testosterone replacement therapy for guidance on adjusting testosterone therapy.

The main limitation of transdermal testosterone patches is skin irritation, which is occurs in about 50% of patients and can be severe. Pretreating the application site with topical hydrocortisone may reduce irritation.

To avoid transferring active drug to another person through skin-to-skin contact, advise thorough hand washing after applying testosterone gel or liquid, covering the application area with clothing, and showering before direct skin contact with others. Repeated inadvertent transfer to another person could increase their serum testosterone concentration and cause adverse effects (eg growth of facial or body hair, deepening of the voice, menstrual irregularities in females, premature puberty and genital enlargement in children).

Note 7: Testosterone 1% gel is available in 25 mg and 50 mg sachets, and in a pump dispensing 12.5 mg per actuation.

Intramuscular testosterone replacement therapy

Intramuscular testosterone replacement therapy

Testosterone injection must be given by deep intramuscular injection; it is not recommended in individuals with bleeding disorders or those receiving anticoagulation. Give the injection very slowly to minimise discomfort, and take care to avoid inadvertent intravenous administration.

For intramuscular testosterone replacement therapy, use:

1 testosterone undecanoate 1000 mg by deep intramuscular injection; repeat after 6 weeks and then every 10 to 14 weeks, according to clinical response and serum testosterone concentration. For more gradual replacement, give the second dose after 10 to 14 weeks *male androgen deficiency, intramuscular therapy*

OR

2 testosterone enantate 250 mg by deep intramuscular injection, every 2 to 3 weeks

OR

2 testosterone esters 250 mg by deep intramuscular injection, every 2 to 3 weeks.

See Monitoring testosterone replacement therapy for guidance on adjusting testosterone therapy.

Although uncommon, coughing, dyspnoea, sweating, chest pain, dizziness, paraesthesia, or syncope can occur during or immediately after injection of testosterone. This has been attributed to pulmonary oil microembolism. Treatment is supportive, and further therapy with intramuscular testosterone is not contraindicated.

Testosterone enantate or testosterone ester injections may be associated with marked fluctuation in testosterone concentration, leading to variation in energy, wellbeing and libido.

Oral testosterone replacement therapy

Oral testosterone replacement therapy

Oral testosterone undecanoate is less effective than other testosterone formulations. It has low (under 10%) and variable bioavailability and a short duration of action, so multiple daily doses are required.

For oral testosterone replacement therapy, use:

testosterone undecanoate 120 to 160 mg orally, daily in 2 divided doses for 2 to 3 weeks. Adjust dose according to clinical response and serum testosterone concentration (usual range 80 mg to 240 mg daily). *male androgen deficiency, oral therapy* _

See Monitoring testosterone replacement therapy for guidance on adjusting testosterone therapy.

Monitoring testosterone replacement therapy

Monitoring testosterone replacement therapy

Overview of monitoring testosterone replacement therapy

Overview of monitoring testosterone replacement therapy

Monitoring testosterone replacement therapy for male androgen deficiency involves reviewing response to therapy (by assessing clinical response and measuring testosterone concentration) and being alert to evidence of adverse events. See Table 20.34 for a summary of monitoring undertaken by a specialist or under specialist guidance.

Table 20.34 Monitoring for clinical response and serious adverse effects of testosterone replacement therapy

Reason for monitoring	Action
	review improvement in symptoms of male androgen deficiency 3 months after starting testosterone, then at least annually
assessing adequacy of testosterone replacement	measure serum testosterone concentration 3 to 6 months after starting testosterone, then as determined by response
	measure bone mineral density 12 months or more after starting testosterone
risk of polycythaemia	review FBE at baseline, 3 months after starting testosterone, then at least annually
	assess baseline risk of prostate cancer
risk of promoting growth in a pre-existing prostate cancer [NB1]	exclude symptoms of prostate cancer
	discuss limitations of PSA screening with asymptomatic men; if PSA screening is chosen, see here for advice on frequency of monitoring
cardiovascular risk in frail older men [NB2]	assess baseline cardiovascular risk factors; review for symptoms of fluid overload

Reason for monitoring	Action

- FBE = full blood examination; PSA = prostate specific antigen
- NB1: For discussion of testosterone replacement therapy and prostate cancer risk, see Monitoring for adverse effects of testosterone replacement therapy.
- NB2: Data on cardiovascular risks of testosterone replacement therapy are conflicting; see Monitoring for adverse effects of testosterone replacement therapy.

Monitoring response to testosterone replacement therapy

Monitoring response to testosterone replacement therapy

Most **symptoms and signs** of androgen deficiency respond within 1 to 2 months of starting treatment. Libido is expected to increase; this may be experienced as either a benefit or an adverse effect by men or their partners. Changes in body composition can occur within 3 to 6 months. Assess bone mineral density every 12 months or more to check that the testosterone dose is adequate for bone maintenance.

Measure **serum total testosterone concentration** 3 to 6 months after starting testosterone, then at intervals determined by clinical response and whether dose modification has been required. If testing is required after a change in dose, it should be performed after at least 2 weeks. Target total testosterone concentrations are in the lower half of the reference range. Timing of measurements depends on the testosterone formulation used:

- for **cream**, measure in the morning predose
- for **1% transdermal gel**, measure in the morning predose
- for **2% transdermal gel**, measure 2 to 4 hours after dose
- for **patches**, measure 3 to 12 hours after application
- for **intramuscular testosterone undecanoate**, measure in the morning just before the third dose after a dose change
- for **short-acting injectable formulations** (testosterone enantate and esters), measure in the morning midway between injections.

Multiple-daily dosing with oral testosterone is not readily monitored with serum testosterone concentrations.

Monitoring for adverse effects of testosterone replacement therapy

Monitoring for adverse effects of testosterone replacement therapy

Adverse testosterone effects include common effects (which can be mild and reversible) or more serious effects, for which monitoring is needed. Table 20.34 includes a summary of monitoring for adverse events.

Common adverse effects from testosterone replacement therapy include truncal seborrhoea and acne (particularly with testosterone ester injections), modest weight gain (under 3 kg) and reduced spermatogenesis. Increased truncal hair, temporal hair loss or balding, and gynaecomastia can also occur. Adverse effects generally reverse when therapy is stopped.

Serious adverse effects from testosterone replacement therapy are uncommon but include polycythaemia, prostate growth, and transient worsening of obstructive sleep apnoea. Risk of cardiovascular events and venous thromboembolism may be increased in men taking testosterone, but evidence to confirm this association is lacking.

Polycythaemia occurs most often with short-acting injectable testosterone (esters and enantate forms). Measure haemoglobin and haematocrit at baseline, then 3 months after starting therapy, then annually. Exclude other causes of secondary polycythaemia (including smoking, obstructive sleep apnoea, and respiratory failure). Polycythaemia is treated by interrupting therapy, dose reduction or increasing the dose interval. Occasionally, venesection is required.

Testosterone therapy reverses the reduced prostate volume and prostate specific antigen (PSA) concentration that occur in male androgen deficiency. This **prostate growth** can lead to elevated prostate specific antigen

(PSA), which, if monitored, may prompt investigation for prostate cancer. There is no association between testosterone replacement and incident prostate cancer, except that men with lifelong untreated androgen deficiency are at reduced risk.

For individuals at substantial risk of pre-existing prostate cancer, measure PSA before starting testosterone therapy. If warranted by symptoms, perform digital rectal examination, or refer for urological assessment. Prostate cancer risk may be increased if any of the following are present:

- prostatic symptoms
- a strong family history [Note 8]
- previous serum PSA concentration more than 4 nanogram/mL.

For asymptomatic men, PSA testing before or during testosterone replacement constitutes prostate cancer screening. Given there is no consensus about population screening for prostate cancer, this issue should be addressed by the testosterone prescriber according to existing guidelines, which support discussing screening in males aged 50 to 69 years at average risk using a decision aid [Note 9].

If prostate screening and monitoring is chosen, at the time of writing, guidelines suggest measuring PSA at baseline, then 3 to 12 months after starting testosterone therapy, then every 2 years.

Risk of **cardiovascular events** may be increased in frail older men taking testosterone, although the evidence for an effect of testosterone is mixed and the association is unconfirmed. The T-Trials cardiovascular trial [Note 10] observed a greater 12-month increase in the primary endpoint, noncalcified coronary plaque volume, in testosterone-treated males, but the clinical relevance of this remains undefined. Assess cardiovascular risk before starting testosterone therapy and manage risk factors as for the general population. Closely monitor older people (particularly those with frailty) and those with cardiovascular disease, kidney failure or severe hypertension. Testosterone therapy can cause fluid overload from sodium and fluid retention, which can exacerbate these conditions.

Note 8: For advice on familial prostate cancer risk, see the Royal Australian College of General Practitioners (RACGP) guideline Genomics in general practice.

Note 9: See the Royal Australian College of General Practitioners (RACGP) guideline on prostate cancer screening.

Note 10: Budoff MJ, Ellenberg SS, Lewis CE, Mohler ER, 3rd, Wenger NK, Bhasin S, et al. Testosterone treatment and coronary artery plaque volume in older males with low testosterone. JAMA 2017;317(7):708-16. [URL]

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[X] Close

Definition and causes of delayed puberty in males

Definition and causes of delayed puberty in males

Delayed puberty in males is defined as the absence of testicular enlargement (ie testicular volume less than 4 mL as assessed using an orchidometer) by age 14 years. Acne, body odour and body hair can occur in the absence of testicular enlargement, and may be due to adrenarche (normal adrenal gland hormonal production). Referral for delayed puberty is not needed before 14 years, unless the male is already known to have an underlying condition that will delay puberty.

Do not refer males younger than 14 years for delayed puberty, unless they are known to have a condition that will cause delay.

Causes of delayed puberty in males include:

- constitutional delay (ie delay in completing spontaneous puberty—a normal variant often associated with a family history of delayed puberty); it is the cause for delayed puberty in most males
- a chronic medical condition, accounting for a small number of cases (differentiation from constitutional delay can be difficult)
- permanent hypogonadotrophic hypogonadism; this is rare and is either idiopathic (including some forms of Kallmann syndrome [Note 1]) or due to hypopituitarism
- primary testicular disorders, such as Klinefelter syndrome [Note 2].

Note 1: For information on Kallmann syndrome, see the US National Library of Medicine Medline Plus website.

Note 2: For information on Klinefelter syndrome, see the US National Library of Medicine Medline Plus website.

Management of delayed puberty in males

Management of delayed puberty in males

Males with delayed puberty resulting from permanent hypogonadotrophic hypogonadism or a primary testicular disorder need lifelong androgen replacement therapy to induce and maintain virilisation; see Male androgen deficiency.

Males with constitutional delay or a chronic medical condition may only need temporary androgen replacement (eg until spontaneous puberty occurs or the underlying condition is managed). Clear distinction between constitutional delay and delay due to chronic illness is difficult in adolescents, and they may represent a spectrum rather than discrete causes.

A decision to start androgen replacement therapy requires specialist evaluation of the physical and psychological effects of the pubertal delay. Fertility is also a consideration in determining when to start replacement. Preliminary data show that fertility outcomes for males with hypogonadotrophic hypogonadism may be improved by early gonadotrophin therapy (human chorionic gonadotrophin [hCG] and follicle stimulating hormone [FSH]) during puberty, ideally undertaken before testosterone therapy. Referral to a specialist centre is needed for gonadotrophin therapy.

Androgen replacement therapy requires specialist guidance because:

- excessive androgen may accelerate epiphyseal maturation, leading to premature epiphyseal closure
- a full adult dose of testosterone in previously untreated males can cause priapism.

Androgen replacement therapy in males with delayed puberty requires specialist guidance on starting and ongoing management.

Androgen replacement therapy is given for 3 months if constitutional delay is suspected, or 6 to 12 months for other potentially reversible causes. This is followed by a break of 3 months to check for spontaneous pubertal development. A typical regimen is:

1 testosterone enantate 50 mg by deep intramuscular injection for the first dose, then 100 mg monthly for subsequent doses *delayed puberty in males*

OR

1 testosterone esters 50 mg by deep intramuscular injection for the first dose, then 100 mg monthly for subsequent doses *delayed puberty in males*

OR

1 testosterone undecanoate 40 mg orally, on alternate days initially, increasing gradually to 120 mg daily. *delayed puberty in males*

If spontaneous pubertal development has not occurred and prolonged treatment is required, the testosterone dose can be gradually increased to the adult dose at a rate that produces the desired speed of maturation. The physical and psychological effects of treatment must be monitored.

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Overview of medical abortion in primary care

Overview of medical abortion in primary care

This topic may be relevant for any person who can conceive; this includes cis women, trans men and nonbinary people.

Medical abortion is achieved by a combination of oral mifepristone (a progesterone receptor blocker) and buccal misoprostol (a prostaglandin analogue), available as a composite pack (mifepristone and misoprostol [MS-2 Step]; see Medical abortion regimen). This regimen induces the miscarriage of an intrauterine pregnancy by:

- preventing progesterone from supporting the pregnancy
- softening and dilating the cervix
- increasing uterine contractility.

In the primary care setting, medical abortion is only approved by the Australian Therapeutic Goods Administration (TGA) for intrauterine pregnancies of up to 63 days' (9 weeks') gestation, also termed 'early medical abortion'. This topic does not cover medical abortion for later gestations.

Medical abortion in primary care is approved for intrauterine pregnancies of up to 63 days' (9 weeks') gestation.

Very early medical abortion refers to medical abortion when an ultrasound has not shown definite evidence of an intrauterine pregnancy. The drug regimens used are the same as for gestations of up to 63 days (9 weeks). Very early medical abortion should only be offered by experienced practitioners, because of the increased risk of an undiagnosed ectopic pregnancy. Alternatively, abortion can be deferred until ultrasound confirms that the pregnancy is intrauterine.

Nondirective counselling about pregnancy options may be beneficial for some individuals, particularly those at increased risk of distress, to assist their decision on whether to proceed with an abortion [Note 1]. It can be undertaken by a suitably trained GP, psychologist, social worker or nurse.

Risk factors for heightened distress associated with abortion include:

- coercion
- personal, family or cultural values conflicting with abortion
- extreme ambivalence about the decision
- lack of support identified by the individual
- underlying issues such as mental health or domestic violence
- a previously wanted pregnancy and changed circumstances.

In making a decision to proceed with a medical abortion, an individual needs an understanding of how it compares to a surgical abortion (outlined in Table 20.21) and a realistic expectation of what is involved; see also Regulatory and legal requirements for medical abortion.

Table 20.21 Comparison of potential advantages of medical and surgical abortion

Medical abortion	Surgical abortion
usually avoids invasive procedures and potential surgical complications (eg uterine perforation, anaesthetic risk) [NB1]	less likely to require subsequent evacuation of retained products [NB1]

Medical abortion	Surgical abortion
may be safer for individuals with obesity or distortion of the uterine cavity	requires only one appointment and is usually performed under sedation
may be more widely accessible	causes less pain; bleeding resolves in a few days rather than weeks
usually less costly	less risk of severe bleeding and access to emergency care not usually required
usually allows abortion to take place at home	avoids potential distress of seeing the gestational sac
seen by some individuals as a more natural and less medical process	

NB1: In 3 to 5% of medical abortions and less than 1% of surgical abortions, subsequent surgical evacuation of retained products of conception is required.

Individuals undergoing abortion (medical or surgical) have an increased risk of future unplanned pregnancy. It is important to discuss contraception as part of the management plan. Contraception may be started at the consultation in which medical abortion drugs are prescribed, or considered at the follow-up consultation. See Contraception after medical abortion for more information.

Note 1: More information on nondirective counselling about pregnancy options is available at the Department of Health website.

Regulatory and legal requirements for medical abortion

Regulatory and legal requirements for medical abortion

Laws governing abortion, including medical abortion, are different in each Australian state and territory. In most jurisdictions, first-trimester abortions are legal on request, although specific legal requirements vary [Note 2].

The mifepristone and misoprostol combination pack is available on the Pharmaceutical Benefits Scheme for medical termination of an intrauterine pregnancy up to 63 days' (9 weeks') gestation. Pharmacists must be individually registered to dispense the mifepristone and misoprostol combination pack.

Providers of medical abortion must be registered with the MS-2 Step Prescribing Program. This requires completion of free online training [Note 3], except for practitioners with a current Fellowship or Advanced Diploma of the Royal Australian and New Zealand College of Obstetricians and Gynaecologists. To find a provider of medical abortion, contact a local family planning organisation.

Written consent is recommended for medical abortion; a template developed by the MS-2 Step program is available. Obtaining **informed consent** for medical abortion requires the registered prescribing practitioner to ensure the individual has a realistic expectation of what will happen and what symptoms require immediate medical attention. It is a prescribing requirement that individuals receive a written outline of this information [Note 4], and a 24-hour telephone helpline number provided by the MS-2 Step program [Note 5]. Urgent clinical assessment and emergency gynaecology admission must be available.

Informed consent requires the individual to understand that:

- the expected effects include bleeding and pain during medical abortion
- normal activities can continue between taking mifepristone and misoprostol (which is taken later) but the person will need to be at home resting with access to a toilet when the misoprostol is taken. Some individuals will be able to return to work the following day (depending on timing of the abortion and symptoms) but others will need an additional 1 to 2 days off work
- complications are uncommon, but the individual needs to recognise when to seek help
- a support person is recommended to be with the individual from the time misoprostol is taken until the heaviest bleeding has settled, to help access emergency treatment if required

- once the medical abortion process has started, it is recommended that it is completed because misoprostol is a known teratogen
- follow-up is important to ensure safety and to establish that the abortion is successful.

Note 2: See the Children by Choice website for more detail.

Note 3: Online training takes approximately 4 hours and is available at the MS-2 Step website.

Note 4: Registered providers can order patient information brochures and consent forms from the MS-2 Step website or download them from the Sexual Health Victoria website.

Note 5: See the MS-2 Step aftercare information.

Contraindications and precautions in medical abortion

Contraindications and precautions in medical abortion

Contraindications to medical abortion in general practice include:

- travel time to hospital emergency services is longer than 2 hours; a small percentage of users experience a haemorrhage or other severe complications in the 14 days following administration of mifepristone
- confirmed or suspected ectopic pregnancy
- intrauterine contraceptive device (IUD) currently in place; mifepristone and misoprostol cause strong uterine contractions, which can cause uterine injury if an IUD is in place. Other risk factors for uterine rupture (including previous caesarean section and other uterine surgery) are not contraindications to medical abortion
- uncertainty about gestational age
- suspected or known haemorrhagic disorders or treatment with anticoagulants
- inherited porphyria; there is a theoretical risk of precipitating or exacerbating attacks of porphyria, but no data are available
- hypersensitivity to mifepristone, misoprostol or any prostaglandin
- long-term use of an oral corticosteroid (eg in chronic adrenal insufficiency, rheumatoid arthritis or difficult-to-control asthma). Mifepristone has antiglucocorticoid effects; its use in individuals taking regular oral corticosteroids is contraindicated without specialist advice. If medical abortion is considered (eg due to competing risks from surgical abortion), seek advice from a specialist regarding the safety of offering medical abortion and the potential need to change corticosteroid dosages.

Precautions for medical abortion in general practice include:

- difficult-to-control asthma—even if not taking long-term oral corticosteroids, seek advice from a specialist or experienced provider of medical abortion about the safety of medical abortion
- well-controlled asthma—if asthma is stable (and long-term oral corticosteroids are not being taken) ensure the individual has an asthma action plan and access to medical services. Long-term inhaled corticosteroid doses may need to be increased for 3 to 4 days after medical abortion because mifepristone has antiglucocorticoid effects
- severe anaemia—seek advice from a specialist or experienced provider of medical abortion about the safety of medical abortion
- epilepsy—seizures have been reported with misoprostol use, but none with medical abortion; caution may be required if there is a history of seizures induced by pain or vomiting
- history of ischaemic heart disease or severe hepatic, kidney or respiratory disease—consult an experienced provider of medical abortion
- diabetes requiring insulin—nausea and vomiting after taking mifepristone and misoprostol may affect poorly controlled diabetes; additional blood glucose monitoring and nausea prevention may be required.

Breastfeeding is not a contraindication to the use of mifepristone and misoprostol.

Investigations before medical abortion

Investigations before medical abortion

Overview of investigations before medical abortion

Overview of investigations before medical abortion

Investigations before medical abortion may be performed by the referring GP or the abortion provider. They include [Note 6]:

- ultrasound scan (transvaginal or transabdominal)
- quantitative serum human chorionic gonadotrophin (hCG) measurement
- blood haemoglobin measurement if there are risk factors for anaemia (eg coeliac disease, vegetarian diet, heavy menstrual bleeding)
- screening for sexually transmitted infections (chlamydia and gonorrhoea) before prescribing, using a self-collected vaginal swab or a first-pass urine sample, so that infection can be treated before medical abortion; see also Sexually transmitted infections. Alternatively, testing can occur on the day of prescribing if the practitioner is confident that prompt treatment will be possible if infection is identified. Treat any positive results as soon as they are available, to minimise the risk of pelvic inflammatory disease.

Before treatment, the provider of medical abortion should perform a baseline quantitative serum hCG measurement, ideally on the day the mifepristone is taken. This is compared with the serum hCG measurement 7 days after the mifepristone is taken; a drop to below 20% of baseline confirms there is no continuing viable pregnancy.

Note 6: Rhesus antibody testing is no longer required before medical abortion because revised guidance from the National Blood Authority and the Royal Australian and New Zealand College of Obstetricians and Gynaecologists (May 2021) states that evidence is insufficient to recommend routine use of Rhesus D immunoglobulin for medical abortion before 10 weeks gestation.

Ultrasound scan before medical abortion

Ultrasound scan before medical abortion

A transabdominal or transvaginal ultrasound scan is routinely recommended before medical abortion to determine gestation and viability, and to confirm that the pregnancy is intrauterine. Although extremely rare, simultaneous ectopic and intrauterine (heterotopic) pregnancies can occur; an ectopic pregnancy is not excluded by confirmation of an intrauterine pregnancy.

Diagnosis of an intrauterine pregnancy on transabdominal or transvaginal ultrasound is usually not possible before 5 weeks' gestation because it requires visualisation of specific structures within the intrauterine gestational sac (either a yolk sac or a fetal pole). If an intrauterine sac without a yolk sac or fetal pole (an empty gestational sac) is seen on a transabdominal ultrasound, a transvaginal ultrasound is necessary. Causes of this 'empty gestational sac' include:

- very early intrauterine pregnancy (yolk sac and fetal pole are rarely seen before 5 weeks' gestation); see also Very early medical abortion
- ectopic pregnancy, which can cause a collection of fluid in the uterus (pseudosac)
- nonviable pregnancy.

Early gestation is the most common reason that an ultrasound shows either an empty uterus or a gestational

sac without a yolk sac or fetal pole, but always consider ectopic or nonviable pregnancy.

If intrauterine pregnancy could not be confirmed by the initial transvaginal ultrasound scan, but the date of the last menstrual period and the serum hCG concentration are consistent with a very early pregnancy, repeat the ultrasound after 1 to 2 weeks. A further serum hCG test may be useful in conjunction with ultrasound to confirm viability or exclude ectopic pregnancy.

If the date of the last menstrual period, serum hCG concentration and ultrasound findings give discrepant estimations of gestation, the risk of a nonviable or ectopic pregnancy is increased. Next steps include:

- informing the individual of the symptoms of ectopic pregnancy
- performing serial transvaginal ultrasound scans and serum quantitative hCG measurements, and monitoring until a diagnosis is established or until specialist review
- considering referral to or consultation with an early pregnancy assessment unit.

If intrauterine pregnancy cannot be confirmed on a transvaginal ultrasound scan, very early medical abortion (VEMA) may be considered by highly experienced providers, bearing in mind that the pregnancy could be ectopic or nonviable. If VEMA is not being performed, management depends on menstrual history and the serum hCG concentration.

Human chorionic gonadotrophin (hCG) testing in medical abortion

Human chorionic gonadotrophin (hCG) testing in medical abortion

A baseline quantitative serum hCG measurement is recommended before medical abortion. This should be repeated 7 days after the mifepristone is taken; a drop to below 20% of baseline confirms there is no continuing viable pregnancy. Measure the baseline quantitative serum hCG on the day (or as soon as possible before) the mifepristone is taken. The serum hCG concentration increases rapidly while the pregnancy is viable; the earlier the gestation, the faster the hCG will rise between baseline measurement and the mifepristone being taken. The fall in serum hCG concentration after medical abortion may require careful interpretation (particularly in early gestations) if the baseline was measured early.

Perform a baseline quantitative serum hCG measurement on the day (or as soon as possible before) mifepristone is taken.

Serum hCG measurement is also useful:

- for very early gestations (less than 5 to 6 weeks) to guide timing of the ultrasound scan for confirmation of intrauterine pregnancy
    - if the hCG is less than 1500 IU/L, an ultrasound should be delayed unless there is a suspicion of ectopic or nonviable pregnancy
    - if the hCG is above 1500 IU/L, a high-quality transvaginal ultrasound will usually detect an intrauterine gestational sac; however, in the absence of a yolk sac or fetal pole this does not confirm an intrauterine pregnancy
    - if the hCG is around 5400 IU/L, there is a 90% likelihood that a high-quality transvaginal ultrasound scan will detect a yolk sac, which confirms an intrauterine pregnancy
- to assist with the diagnosis of nonviable and ectopic pregnancies in conjunction with serial ultrasounds.

If access to blood testing is difficult, a low-sensitivity urinary hCG test, taken at least 2 weeks after the dose of mifepristone, can be considered instead of baseline and follow-up quantitative serum hCG measurements. See Follow-up after medical abortion for more information.

Medications used in medical abortion

Medications used in medical abortion

Premedication and supportive treatment in medical abortion

Premedication and supportive treatment in medical abortion

Premedication and supportive treatment are prescribed by providers of medical abortion to minimise the expected pain and nausea after taking mifepristone and misoprostol.

Most individuals undergoing medical abortion experience pain, so **analgesia** is usually required. Evidence is insufficient to support choice of one analgesic regimen over another; consider patient preference and previous experience with pain. A **nonsteroidal anti-inflammatory drug** (eg ibuprofen) is usually given before misoprostol (unless contraindicated). An oral **opioid** should be discussed with all individuals undergoing medical abortion. Consider giving prophylactically 30 to 60 minutes before misoprostol. For analgesic dosages, see Oral drugs for moderate acute nociceptive pain in adults.

Offer an **antiemetic** (eg ondansetron, metoclopramide) before both mifepristone and misoprostol, especially if pregnancy-induced nausea or vomiting is present; see Antiemetic drugs for dosages.

Medical abortion regimen

Medical abortion regimen

Medical abortion is achieved by a combination of mifepristone and misoprostol, available as a composite pack (mifepristone and misoprostol [MS-2 Step]). Pharmacists must be individually registered to dispense this composite pack and may not always carry stock, so it is recommended that prescribers are aware of, or contact, local registered pharmacists when prescribing. Registered prescribers can access the location of registered pharmacists from the MS-2 Step website.

Mifepristone blocks the action of progesterone, the hormone necessary for a continuing pregnancy. It also softens and dilates the cervix, and increases uterine activity (by increasing prostaglandin concentrations and uterine sensitivity to prostaglandins).

Misoprostol is a synthetic prostaglandin E1 analogue that increases uterine contractility and softens the cervix. Both effects are enhanced by giving a preceding dose of mifepristone. Misoprostol is given buccally; oral dosing is less effective and causes more gastrointestinal adverse effects (eg nausea and vomiting).

To induce medical abortion, use:

mifepristone 200 mg orally *medical abortion*

FOLLOWED BY

misoprostol 800 micrograms buccally, 36 to 48 hours after taking mifepristone. Moisten the mouth, then place 2 tablets (400 micrograms) on **each** side between the teeth and the gums and hold in place for 30 minutes. Remaining tablet fragments may be swallowed with a glass of water. *medical abortion*

If vomiting occurs within 1 hour of mifepristone administration, provide a repeat prescription for mifepristone and misoprostol, with an antiemetic administered beforehand.

In 5% of individuals, products of conception may be expelled in the time between taking mifepristone and misoprostol. Misoprostol should be taken regardless of bleeding or produce expulsion to minimise the risk of retained products of conception.

Normal activities can continue between taking mifepristone and misoprostol, but the individual will need to be at home, resting, with access to a toilet on the day misoprostol is taken. They may need an additional 1 to 2 days off work (depending on timing of the abortion and symptoms). A support person is recommended to be with the individual from the time misoprostol is taken until the heaviest bleeding has settled, to help access emergency treatment if required. For 14 days after taking mifepristone, the individual needs to be within 2 hours travel time of hospital emergency services, in case of haemorrhage or other complications.

Shorter dosing intervals (24 to 36 hours between taking mifepristone and misoprostol) can be used but are not licensed by the Australian Therapeutic Goods Administration (TGA). A shorter interval can be considered

for practical reasons (eg to allow the timing of the bleeding to occur when a support person is available). However, limited data suggest that a 24-hour interval may slightly increase the risk of retained products of conception, particularly for gestations of 50 to 63 days.

Effects of medical abortion

Effects of medical abortion

Effects expected after taking mifepristone

Effects expected after taking mifepristone

After taking mifepristone, a small proportion of individuals experience cramping and light bleeding.

In 5% of users, the products of conception are expelled in the time between taking mifepristone and misoprostol; misoprostol should be taken regardless of bleeding or product expulsion, to minimise the risk of retained products of conception.

Expected effects after taking misoprostol

Expected effects after taking misoprostol

Central lower abdominal **cramping** usually begins within 2 hours of taking misoprostol, and almost always begins within 4 hours. The pain is usually more severe than dysmenorrhoea; the median pain score is 6 out of 10 on a visual analogue scale. It generally decreases once the products of conception are passed (usually within 4 hours of taking misoprostol) but can persist for several days. If pain persists or worsens a week or more after taking misoprostol, consider the possibility of infection.

Bleeding usually starts after cramping. It is expected to be heavier than the regular menstrual period, and clots are typically passed. The gestational sac is not usually observed, but is more likely with later gestations; this can be distressing. Bleeding decreases after the products of conception are passed, but can continue similar to heavy days of the regular menstrual period for 5 to 7 days. Bleeding usually stops by day 14, although it can persist for 4 to 5 weeks. Atypical bleeding may indicate a complication of medical abortion.

Adverse effects of medical abortion

Adverse effects of medical abortion

Mifepristone can cause short-term nausea, vomiting and anorexia. If vomiting occurs within 1 hour of administration, provide a repeat prescription for mifepristone and misoprostol, with an antiemetic administered beforehand.

Although misoprostol can cause nausea and vomiting (as well as transient fevers, chills and diarrhoea), vomiting does not significantly alter its effectiveness because it is absorbed buccally, provided the tablets do not fall out of the mouth during vomiting.

Complications of medical abortion are not common; see Overview of complications of medical abortion for more information. Ensure individuals are informed of symptoms that require medical attention.

Advice for individuals having medical abortion

Advice for individuals having medical abortion

Providers of medical abortion must supply individuals with a written outline of the symptoms they may experience, and a list of symptoms that need urgent medical review [Note 7]. They should be given a 24-hour helpline phone number (see the MS-2 Step aftercare information). Access to hospital emergency services

must be available (within 2 hours travel time) for 14 days after mifepristone is taken. Advise the individual that once a medical abortion has started, it should be completed.

Mifepristone and misoprostol are safe to use during breastfeeding. Advise that it is not necessary for breastmilk to be expressed and discarded.

Provide a pathology request form for a follow-up quantitative serum human chorionic gonadotrophin (hCG) measurement, to be taken 7 days after the mifepristone dose. Emphasise the importance of this test to confirm there is no continuing viable pregnancy. Explain that the presence of bleeding does not always indicate that the treatment has been successful. Ensure recall and reminders are in place to confirm that the test has been performed.

If access to blood testing is difficult, a low-sensitivity urinary hCG test, taken at least 2 weeks after the dose of mifepristone, can be considered instead of baseline and follow-up quantitative serum hCG measurements. See Follow-up after medical abortion for more information.

Table 20.22 Advice after a medical abortion: patient information

Printable table

General advice after a medical abortion

A follow-up blood test is very important to check that the abortion has been successful. The test needs to be taken 7 days after you took the first tablet (mifepristone). Other forms of testing may be appropriate for some people, but your clinic will discuss these with you if they are an option.

For 7 days after taking the second tablet (misoprostol), to reduce the risk of infection, avoid:

- sexual intercourse
- use of tampons or menstrual cups
- swimming
- taking a bath or using a spa.

When to go to an emergency department

Go to an emergency department if at any time you have:

- very heavy bleeding, such as **any** of the following:
  - your bleeding fills more than two large pads in an hour for more than 2 hours in a row
  - you are passing clots the size of a small lemon or larger
  - you feel faint and think the bleeding is heavy even if you are not sure about how much you are bleeding
- **any** of the following symptoms (which could mean an ectopic pregnancy in the Fallopian tube):
  - severe abdominal (tummy) pain
  - pain in your pelvis on one side
  - pain in the tips of your shoulders
- other concerns and you don't have access to medical advice (eg from the prescribing clinic).

When to contact the clinic that prescribed the abortion drugs

If you have any of the symptoms below, you might still be pregnant. Contact the clinic if:

- **at 24 hours** after taking misoprostol, you either:
  - have had no or little bleeding (less than a normal period), or
  - have not passed any pregnancy tissue, or any clots larger than a small grape
- **at 48 hours** after taking misoprostol, you still have nausea
- you had some initial bleeding, but it stopped within **4 days** of taking misoprostol
- **at 14 days** after taking misoprostol, you still have breast tenderness.

If you have any of the symptoms below, there might still be some pregnancy tissue (eg placenta) in the uterus (womb). Contact the clinic if:

- **at 7 days** after taking misoprostol:
  - you are still passing clots
  - you still have cramping pain
  - you still have bleeding that is heavier than a period
  - you have bleeding that stopped and restarted and has been as heavy as a period for the last 24 hours or more
- **at 14 days** after taking misoprostol you have bleeding that is not much less than when it started
- **at 4 to 5 weeks** after taking misoprostol you still have bleeding that is different to your usual menstrual cycle.

Contact the clinic if you have any of the symptoms below, as they can indicate that you have an infection of the uterus:

- pelvic pain
- pain during sex
- unusual vaginal discharge
- fever (over 38°C)
- tenderness on touching the abdomen (tummy) or pelvis
- nausea or vomiting
- feeling unwell.

Contact the clinic that prescribed the abortion drugs if you have any concerns about the medical abortion.

Note 7: Registered providers can order patient information brochures from the MS-2 Step website or the Sexual Health Victoria website.

Follow-up after medical abortion

Follow-up after medical abortion

Follow-up after medical abortion is important to confirm that there is no continuing viable pregnancy or other complications. Usual follow-up involves contact 2 to 4 days after mifepristone is taken in order to:

- check that bleeding is as expected and pregnancy symptoms are resolving
- remind individuals about symptoms that require review
- emphasise the need for the follow-up test to confirm that there is no continuing viable pregnancy.

Further recommended follow-up involves:

- a quantitative serum human chorionic gonadotrophin (hCG) measurement 7 days after taking mifepristone, to confirm that there is no continuing viable pregnancy (confirmed by a drop to below 20% of baseline)
- a review at 14 to 21 days in person, or by phone or telemedicine to check for signs and symptoms of complications, and to review contraceptive needs and emotional wellbeing.

A serum quantitative hCG measurement higher than 20% of the baseline value usually warrants a pelvic ultrasound to assess possible causes, including:

- continuing pregnancy
- retained products of conception
- rare causes such as:
  - heterotopic (concurrent ectopic) pregnancy
  - trophoblastic disease
  - placenta accreta.

Measure quantitative serum hCG 7 days after the mifepristone was taken; a fall to below 20% of baseline

confirms the individual does not have a continuing viable pregnancy.

Standard urinary hCG tests (which give a positive result if urinary hCG concentration is more than 25 IU/L) have a limited place in follow-up because they often remain positive for many weeks after abortion; they may be considered if follow-up has been delayed for a month or more.

A low-sensitivity urinary hCG test (such as Check4 HCG) can be an alternative to follow-up serum testing, particularly if access to blood testing is difficult; a baseline measure is not required. It should be performed at least 2 weeks after taking mifepristone. A negative test excludes continuing pregnancy in almost all cases in which an intrauterine pregnancy was confirmed on ultrasound. A positive test (indicating a urinary hCG concentration of more than 1000 IU/L) requires follow-up with a quantitative serum hCG measurement, and may also require an ultrasound. False positives may occur if the test is done too early or may indicate conditions such as trophoblastic disease.

Ultrasound is not routinely advised to assess the outcome of medical abortion if there are no symptoms suggestive of complications, because it risks false positive findings that may trigger unnecessary surgical intervention.

Most individuals report feeling a range of emotions after medical abortion, including relief, sadness and guilt. Evidence does not support an association with serious mental health outcomes, but ongoing support may be required. Consider referral to a psychologist, social worker or psychiatrist.

Overview of complications of medical abortion

Overview of complications of medical abortion

Complications and their presentation are outlined in Table 20.23. Individuals should be informed about the risk of complications as part of the consenting process, and understand when to seek medical attention (see Table 20.22).

Figures for complication rates vary because definitions are imprecise, other than for continuing viable pregnancy. Large studies examining complications often include medical abortions of gestations beyond 9 weeks. Most complications present as atypical bleeding that is heavier or more persistent than expected.

Complications of medical abortion include:

- retained products of conception—3 to 5% of individuals require surgical intervention; rates of retained products treated either with expectant management or repeat doses of misoprostol are unknown
- continuing pregnancy—affects 0.8% of individuals and must be considered if expected bleeding does not occur or other symptoms of pregnancy persist
- haemorrhage—0.13% of individuals experience a haemorrhage requiring a blood transfusion
- upper genital tract infection—affects an estimated 0.11% of individuals.

Other rare causes for atypical bleeding after medical abortion are heterotopic pregnancies (concurrent ectopic pregnancy), trophoblastic disease or placenta accreta; these may not have been visible on the initial ultrasound scan.

Complications should be triaged and managed (if feasible) by the provider of medical abortion. People who present to their general practitioner should be discussed with the provider, if possible. In an emergency, advise (or organise for) review in an emergency department.

Table 20.23 Complications of medical abortion

Complication	Symptoms and presentation
retained products of conception	**7 days after misoprostol:** • bleeding is heavier than the normal menstrual period or contains clots • cramping persists

Complication	Symptoms and presentation
continuing pregnancy	• bleeding settled but restarted and has been as heavy as the person's normal period for at least the past 24 hours **14 days after misoprostol** bleeding has not reduced markedly from its start **4 to 5 weeks after misoprostol** bleeding is still ongoing **infection may also be present** **24 hours after misoprostol:** • bleeding is absent or less than a normal period • no products of conception and no clots larger than a small grape have been passed [NB3] initial bleeding has stopped within **4 days of taking misoprostol** **48 hours after misoprostol,** nausea persists **14 days after misoprostol,** breast tenderness persists **at any time, symptoms of ectopic pregnancy are present:** • severe abdominal pain • unilateral pelvic or shoulder tip pain • onset of weakness • heavy bleeding
haemorrhage [NB1]	**at any time during or after medical abortion:** • bleeding fills more than two pads per hour for 2 consecutive hours • clots are passed the size of small lemons or larger • the individual feels faint or perceives the bleeding as heavy
infection [NB2]	pelvic pain pain during sex unusual vaginal discharge fever (over 38°C) nausea vomiting diarrhoea feeling generally unwell uterine or abdominal tenderness

NB1: Haemorrhage can be caused by retained products, but uncommon causes such as concurrent ectopic pregnancy, trophoblastic disease or placenta accreta must be considered.

NB2: Infection is usually accompanied by retained products but can occur independently.

NB3: This is particularly indicative of continuing pregnancy for gestations of 7 weeks or more.

Retained products of conception after medical abortion

Retained products of conception after medical abortion

Overview of retained products of conception after medical abortion

Overview of retained products of conception after medical abortion

Retained products of conception are nonviable placental or fetal tissue that remains in the uterus even though the individual is no longer pregnant. This is the most common complication of medical abortion. Prolonged or heavy bleeding should be investigated for suspected retained products. See also Table 20.23 for more detail of symptoms and presentation of retained products of conception. If retained products are not expelled (naturally or with further treatment), they can cause chronic bleeding, pain and intrauterine adhesions and fibrosis.

Management options are expectant management, medical management or surgical evacuation; choice of management depends on the degree of bleeding, the risk of anaemia and patient preference for management.

Investigations for suspected retained products of conception

Investigations for suspected retained products of conception

Retained products of conception is usually a clinical diagnosis based on bleeding patterns. The presentation varies and clinical judgment is required to determine if and when intervention is required. Input from an experienced practitioner may be needed.

If symptoms of retained products are present, and the individual does not have haemorrhage requiring emergency management, examine the cervix and remove any clots that are present.

Further investigations are not routinely required if all of the following are present:

- the serum hCG concentration dropped to below 20% of baseline
- the bleeding is light or only intermittently moderate
- there is no clinical suspicion of anaemia
- the individual is well.

Investigations are required if the bleeding is heavier than expected at any stage after the medical abortion. Check the **full blood count and iron studies** to assess the degree of blood loss and detect moderate to severe anaemia and guide management. Compare the results with baseline studies if available.

An ultrasound scan can be useful to assess the presence of retained products of conception, but a scan earlier than 3 weeks post misoprostol is unlikely to be helpful—blood clots are likely to be present and can interfere with interpretation. However, an ultrasound should not be delayed if a continuing pregnancy is suspected. Consistent guidelines for determining the significance of retained products (by volume and features, including vascularity), are lacking, and case-by-case interpretation is required, based on clinical features and ultrasound findings.

If the ultrasound scan shows significant retained products of conception, surgical evacuation may be indicated; refer for specialist assessment.

If the ultrasound scan does not show significant retained products of conception, bleeding is likely to resolve spontaneously. Support the individual to make an informed choice between expectant management or medical management, with the option of surgical evacuation as backup. Also manage any concurrent infection.

Expectant management of retained products of conception

Expectant management of retained products of conception

Expectant management of retained products of conception involves ongoing review to monitor bleeding, symptoms of infection and general health.

A minority of individuals with retained products after medical abortion have an elevated serum hCG concentration (above 20% of the baseline value) 7 days after taking mifepristone. If an ultrasound scan has excluded a continuing intrauterine pregnancy but shown retained products, serial serum hCG measurements are useful to confirm that the elevated concentration is falling. If it is not falling, consider other diagnoses (eg ectopic pregnancy, trophoblastic disease) and refer for specialist management.

Ensure that the individual has written instructions on symptoms requiring medical attention; see Table 20.22.

If moderate bleeding persists at 3 to 4 weeks, consider a repeat ultrasound scan and specialist advice.

If bleeding is becoming lighter and only spotting persists at 4 to 5 weeks after medical abortion, no further intervention is needed.

Medical management of retained products of conception

Medical management of retained products of conception

Medical management of retained products of conception is an option if bleeding is moderate and the individual prefers active to expectant management. It involves repeat dosing of misoprostol as a single drug along with premedication and analgesia. A suitable regimen is [Note 8]

misoprostol 400 micrograms buccally. Moisten the mouth, then place one tablet (200 micrograms) between the teeth and the gums on each side of the mouth and hold them in place for 30 minutes. Remaining tablet fragments may be swallowed with a glass of water. Repeat the 400 microgram dose after 4 hours if no significant bleeding has occurred. *medical abortion, retained products of conception*

Ensure the individual has a support person and access to emergency services. Organise a follow-up phone or in-person assessment 24 to 48 hours after the last dose of misoprostol. Ensure they have written instructions on symptoms requiring medical attention; see Table 20.22.

If medical management is unsuccessful, options are expectant management by an experienced provider or surgical evacuation.

Note 8: Misoprostol is available as a single-ingredient formulation; combination with mifepristone is not required or advised for this situation.

Surgical evacuation of suspected retained products of conception

Surgical evacuation of suspected retained products of conception

Surgical evacuation is a first-line option for management of suspected retained products of conception if the individual:

- has haemorrhage; consider the need for emergency management
- has significant retained products of conception confirmed on ultrasound combined with any of:
  - moderate to heavy bleeding
  - mild anaemia
  - concurrent infection
- has heavy ongoing bleeding even if retained products are not visible on ultrasound
- has moderate to severe anaemia; refer for urgent ultrasound to establish extent of retained products and arrange a gynaecological consultation
- prefers surgery to expectant or medical management.

Surgical evacuation can also be considered if bleeding persists after expectant or medical management.

Surgical evacuation is required in 3 to 5% of individuals who undergo medical abortion.

Suspected continuing pregnancy after medical abortion

Suspected continuing pregnancy after medical abortion

Continuing pregnancy occurs in around 0.8% of people undergoing medical abortion. It is suspected if bleeding is absent or lighter than expected or pregnancy symptoms are present. Indicators include:

- at 24 hours after misoprostol:
    - bleeding is absent or less than a normal period
    - no clots (or only those less than grape size) have been passed
    - no products of conception passed (especially if gestation is 7 weeks or more)
- initial bleeding has stopped within 4 days of taking misoprostol
- other indicators:
    - symptoms of pregnancy persist: nausea still present at 48 hours after misoprostol or breast tenderness persists at 14 days
    - serum hCG concentration increases above baseline or shows a small relative drop at 7 days after mifepristone is taken (rather than falling to below 20% of baseline level, as expected with a successful medical abortion).

Consider the possibility of ectopic pregnancy, which requires emergency management. If an intrauterine pregnancy was confirmed on the ultrasound scan performed before the abortion, the likelihood of a concurrent ectopic pregnancy is extremely low. Symptoms of an **ectopic pregnancy** include:

- severe abdominal pain
- unilateral pelvic or shoulder tip pain
- onset of weakness
- heavy bleeding.

In all individuals with suspected continuing pregnancy, order a repeat ultrasound scan.

If the repeat ultrasound confirms ongoing intrauterine pregnancy, advise completing the abortion process because misoprostol is a known teratogen.

If the pregnancy is 63 days' (9 weeks') or less gestation, a repeat dose of mifepristone and misoprostol, or surgical abortion are options. If the repeated mifepristone and misoprostol is unsuccessful, organise surgical abortion.

If the pregnancy is over 63 days' gestation, organise a surgical abortion.

If the individual indicates an intention to continue the pregnancy, specialist referral is recommended.

If intrauterine pregnancy is not confirmed on the repeat ultrasound scan, but retained products of conception are visible, manage as for retained products of conception. If neither intrauterine pregnancy nor retained products are visible, seek specialist advice.

Haemorrhage after medical abortion

Haemorrhage after medical abortion

Haemorrhage is usually caused by retained products of conception, but uncommon causes (eg concurrent ectopic pregnancy, trophoblastic disease and placenta accreta) must be considered. If any of the following features is present at any time during or after medical abortion, immediate transfer to an emergency department is required:

- bleeding filling more than two large pads per hour for more than 2 hours in a row
- passing clots the size of a small lemon or larger
- feeling faint and perceiving the bleeding as heavy, even if the individual is not sure of the amount of blood being lost.

Emergency management may include blood transfusion; this is required in 0.13% of individuals after medical abortion.

Infection after medical abortion

Infection after medical abortion

Infection of the upper genital tract after medical abortion occurs in around 0.11% of people undergoing medical abortion. However, international estimates vary from less than 0.1% (for severe infection requiring intravenous antibiotics in hospital) to 1% (for infections requiring treatment with oral antibiotics).

Infection generally presents later than 7 days after misoprostol is taken and can be associated with retained products of conception or an untreated sexually transmitted infection (STI). Unrecognised infection can progress to ascending infection and subsequent tubal scarring, or life-threatening sepsis.

Suspect infection if any of the following symptoms or signs are present:

- abdominal pain or tenderness
- abnormal vaginal discharge
- dyspareunia
- feeling unwell
- nausea, vomiting or diarrhoea
- temperature higher than 38°C
- uterine tenderness.

Refer immediately to an emergency department for moderate to severe infection. Features of moderate to severe infection include:

- lack of response to initial antibiotics
- severe pain
- systemic features (eg fever of at least 38°C, tachycardia, vomiting)
- sepsis or septic shock.

If results of screening tests for STIs performed before medical abortion were positive, or if an STI cannot be reliably excluded (eg if an STI could have been contracted since screening), treat as for pelvic inflammatory disease.

If an STI can be reliably excluded (ie results of STI screening were negative after an appropriate incubation period, and a subsequent STI could not have been contracted [eg no sexual activity since screening]), treat as for postpartum endometritis.

Special considerations in medical abortion

Special considerations in medical abortion

Nonviable pregnancy

Nonviable pregnancy

Nonviable pregnancy is suggested or confirmed by ultrasound scan [Note 9] in conjunction with the date of the last menstrual period and quantitative human chorionic gonadotrophin measurements. Management options are expectant management, medical management (with either mifepristone and misoprostol, or

misoprostol alone) or surgical management. Nonviable pregnancy is ideally managed in an early pregnancy assessment service.

Note 9: For radiological features of nonviable pregnancy, see the Radiopedia website.

Multiple gestation pregnancy and medical abortion

Multiple gestation pregnancy and medical abortion

Multiple gestation pregnancy is not a contraindication to medical abortion; however, for gestations close to 63 days, the amount of tissue to pass is large, so a surgical abortion may be preferred.

Very early medical abortion

Very early medical abortion

Very early medical abortion (VEMA) refers to medical abortion when an ultrasound has not shown definite evidence of an intrauterine pregnancy (no evidence of a yolk sac or fetal pole in an intrauterine sac). This finding is termed a 'pregnancy of unknown location' (PUL) because the pregnancy may be intrauterine (but not yet visible) or ectopic.

Advantages of very early medical abortion include avoiding delay and reducing the risk of retained products of conception. It may also cause less pain and bleeding than later medical abortion, although evidence is currently lacking. Drug regimens used for very early medical abortion are the same as for gestations of up to 63 days (9 weeks) (see Medical abortion regimen).

Very early medical abortion should only be offered by experienced practitioners, because of the potentially increased risk of an undiagnosed ectopic pregnancy. Alternatively, medical abortion can be deferred until ultrasound confirms that the pregnancy is intrauterine.

Very early medical abortion of PUL should only be offered by experienced practitioners who have clear follow-up protocols in place. Follow-up is critical to limit the risk of undetected ectopic pregnancy.

Very early medical abortion should not be undertaken if:

- there are risk factors for ectopic pregnancy (eg previous ectopic pregnancy, intrauterine contraceptive device in place, a history of pelvic inflammatory disease or tubal surgery)
- there are signs or symptoms of ectopic pregnancy (severe abdominal pain, unilateral pelvic or shoulder tip pain, onset of weakness, heavy bleeding)
- the gestation estimated by dates is incompatible with the quantitative serum human chorionic gonadotrophin (hCG) measurement and the first ultrasound; see Ultrasound scan before medical abortion. An absent intrauterine sac on transvaginal ultrasound and a serum hCG measurement more than 1500 IU/L suggest an ectopic pregnancy; urgently refer to a specialist
- the individual is unable to provide informed consent or comply with early follow-up.

Experienced practitioners must assess the possibility of an ectopic pregnancy on a case-by-case basis, and ensure close monitoring and follow-up. Management protocols should include:

- clear advice to seek immediate medical attention if symptoms or signs of an ectopic pregnancy occur
- follow-up by phone or in person within 3 days (see Follow-up after medical abortion)
- a repeat quantitative serum hCG measurement in 3 to 5 days after mifepristone is taken.

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Definition of male androgen deficiency

Definition of male androgen deficiency

This topic covers management of androgen deficiency in cis men; for advice on gender-affirming hormone therapy and gender-inclusive primary healthcare, see resources for trans and gender diverse health care. For information on androgen deficiency in childhood, see Delayed puberty in males.

Male androgen deficiency is defined as impaired testosterone production (due to proven dysfunction in the hypothalamic–pituitary–testicular [HPT] axis) that causes symptoms or effects on target organs.

Male hypogonadism is male androgen deficiency accompanied by impaired fertility; it may be:

- **hypergonadotrophic**—caused by primary (testicular) disorders that reduce testosterone production and spermatogenesis; these, in turn, reduce negative feedback on gonadotrophin (luteinising hormone [LH] and follicle stimulating hormone [FSH]) production, leading to increased gonadotrophin concentrations
- **hypogonadotrophic**—caused by a central (hypothalamic or pituitary) disorder that reduces production of gonadotrophins, diminishing stimuli to the testis to produce hormones and sperm.

For treatment of infertility in male hypogonadism, see Gonadotrophin therapy for male infertility.

Causes of male androgen deficiency

Causes of male androgen deficiency

Primary male androgen deficiency causes symptoms or signs of androgen deficiency, low serum testosterone concentration and elevated serum luteinising hormone (LH) concentration. It results from testicular disorders, including:

- Klinefelter syndrome [Note 1]
- cryptorchidism
- orchidectomy
- orchitis
- cytotoxic or radiation damage to the testes
- testicular torsion or trauma
- androgen synthesis inhibitors.

Central androgen deficiency causes symptoms or signs of androgen deficiency and low serum testosterone and LH concentrations. It results from hypothalamic or pituitary disorders, including hyperprolactinaemia.

- pituitary tumours
- pituitary surgery or radiotherapy
- haemochromatosis, which can cause iron deposition in the hypothalamus and pituitary
- hypophysitis
- idiopathic hypogonadotrophic hypogonadism (including Kallmann syndrome, notable for reduced or absent sense of smell [Note 2]
- gonadotrophin-releasing hormone (GnRH) analogues.

Conditions to be distinguished from central androgen deficiency include:

- exogenous synthetic androgen use

- recent acute illness and convalescence
- functionally low testosterone concentrations.

Use of **exogenous synthetic androgens** may result in a biochemical picture that is similar to central androgen deficiency, but without the expected clinical signs of androgen deficiency; see History and examination.

Recent acute illness and convalescence can cause temporary hypothalamic–pituitary–testicular axis suppression.

Also consider the possibility of functionally low serum testosterone concentration , in which total serum testosterone concentration is usually only mildly reduced in men with comorbidities.

Note 1: For information on Klinefelter syndrome, see the US National Library of Medicine Medline Plus website.

Note 2: For information on Kallmann syndrome, see the US National Library of Medicine Medline Plus website

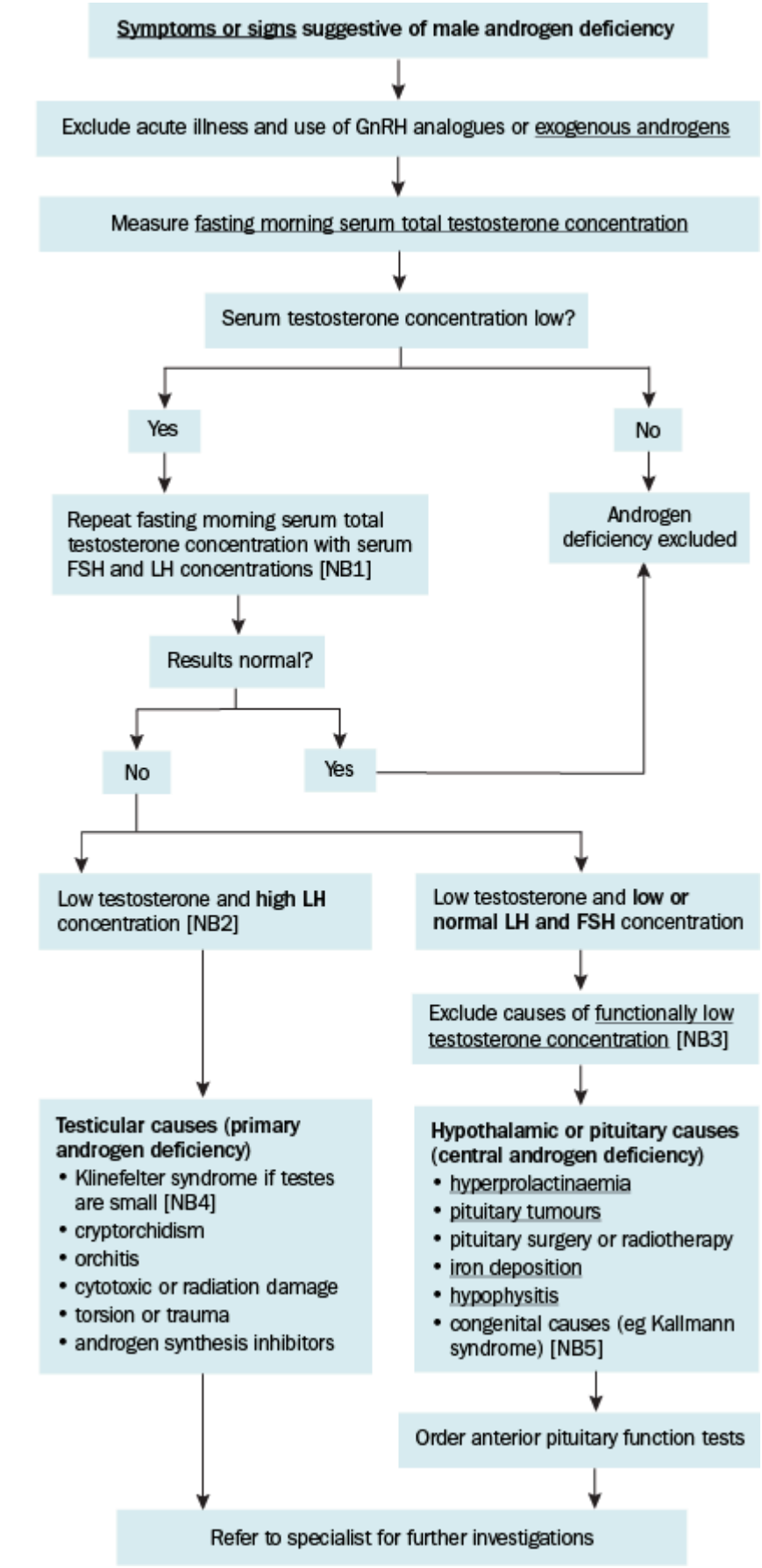
Overview of diagnosis of male androgen deficiency

Overview of diagnosis of male androgen deficiency

Figure 20.14 outlines an approach to diagnosis in suspected androgen deficiency. The aims are to:

- determine whether criteria for androgen deficiency are met
- exclude differential diagnoses
- undertake initial investigations to seek the cause of androgen deficiency (if feasible) before referral.

Figure 20.14 Approach to diagnosis in suspected male androgen deficiency



FSH = follicle stimulating hormone; GnRH = gonadotrophin-releasing hormone; LH = luteinising hormone

NB1: Serum FSH concentration may be easier to interpret than LH, as LH is pulsatile. Serum FSH concentration is also part of assessment for male infertility, which can accompany some causes of androgen deficiency.

NB2: Low testosterone and slightly elevated LH concentrations may be due to normal ageing; see Interpreting serum testosterone concentrations..

NB3: Mildly low testosterone and normal LH concentrations may be due to comorbidities such as obesity, diabetes, depression, or use of opioids, high-dose corticosteroids, alcohol or marijuana; see Interpreting serum testosterone concentrations.

NB4: For information on Klinefelter syndrome, see the US National Library of Medicine Medline Plus website.

NB5: For information on Kallmann syndrome, see the US National Library of Medicine Medline Plus website.

History and examination in male androgen deficiency

History and examination in male androgen deficiency

Androgen deficiency should not be diagnosed unless symptoms and signs are found on history and examination. Many symptoms of androgen deficiency are nonspecific.

Symptoms and signs most likely to indicate androgen deficiency include reduced libido, decreased spontaneous erections, hot flushes, reduced facial hair growth, breast discomfort or gynaecomastia, loss of axillary and pubic hair, small testes (especially volume under 5 mL, assessed using an orchidometer) and low bone mass (particularly low Z-scores). Very small testes are a feature of Klinefelter syndrome [Note 3], which is often missed unless a testicular examination is performed.

Examine men with suspected androgen deficiency for small testes.

Less specific symptoms and signs of androgen deficiency include decreased energy, motivation, concentration, memory or work performance; low mood; disturbed sleep or increased sleepiness; reduced muscle bulk and strength; increased body fat or body mass index; and mild anaemia. Many of these features may be seen with different diagnoses associated with low serum testosterone, such as:

- functionally low serum testosterone concentration
- acute illness.

Rather than typical signs of androgen deficiency (although testicular shrinkage is a feature), use of exogenous androgenic steroids may cause truncal acne and marked muscular development. Ask directly about the use of exogenous synthetic androgens (including unregulated supplements, which may contain unrecognised ingredients).

Ask directly about the use of exogenous androgens, including the use of unregulated supplements.

Note 3: For information on Klinefelter syndrome, see the US National Library of Medicine Medline Plus website.

Interpreting serum testosterone concentrations in diagnosis of male androgen deficiency

Interpreting serum testosterone concentrations in diagnosis of male androgen deficiency

A low serum testosterone concentration must be interpreted in the context of the man's clinical features. For a diagnosis, the following **criteria for diagnosing male androgen deficiency** must all be met:

- symptoms or signs are consistent with male androgen deficiency
- unequivocally low fasting early morning total serum testosterone concentration, confirmed by repeat measurement on a different day

- hypothalamic–pituitary–testicular (HPT) axis dysfunction confirmed.

Serum testosterone concentrations have a wide diurnal variation and are highest in the morning. Samples must be taken between 8 am and 10 am [Note 4], after overnight fasting and confirmed by a repeat measurement on a different day.
Low serum testosterone concentration must be confirmed by repeating the measurement.

Systemic illness temporarily lowers testosterone concentrations and can confound assessment of symptoms. Testosterone should not be measured during an acute illness or convalescence.

Do not measure serum testosterone concentration during an acute illness or convalescence.

Reference ranges for total serum testosterone concentration vary because of factors such as assay method and age. Published ranges relate to mass spectrometry but at the time of writing most laboratories in Australia use immunoassays, so in practice, local reference ranges are used [Note 5].

Some conditions, such as obesity, diabetes and depression, and use of opioids or glucocorticoids, cause a mild reduction in total serum testosterone concentration that does not amount to androgen deficiency, and is generally managed by treating the underlying condition. This finding is referred to as **functionally low total serum testosterone concentration**. Serum gonadotrophin (luteinising hormone [LH] and follicle stimulating hormone [FSH]) concentrations are usually normal; this is consistent with mild functional central suppression of the HPT axis. The underlying conditions may also cause:

- confounding symptoms that overlap with those of androgen deficiency (particularly the less specific features) but are not usually a result of the low testosterone concentration
- reduced hepatic synthesis of sex hormone–binding globulin ([SHBG], the main protein that binds testosterone)—particularly in men with obesity, insulin resistance or glucocorticoid use. This can reduce the total serum testosterone concentration without necessarily affecting the amount of unbound (free) testosterone or having a clinical impact.

Some laboratories report **free serum testosterone concentrations** (calculated using the total serum testosterone and SHBG concentrations). Neither calculations nor reference ranges for free serum testosterone are established. A low free serum testosterone concentration (without a low total serum testosterone concentration) does not warrant testosterone therapy because evidence of clinical benefit is lacking.

If there is uncertainty about the interpretation of serum testosterone concentrations, seek specialist advice.

Note 4: For shift workers or sleep-deprived men, measure testosterone shortly after waking.

Note 5: When assayed by mass spectrometry (not immunoassay which is used by most laboratories), the lower limit for total serum testosterone in males aged 21 to 35 years with normal sexual and reproductive function is 10.4 nanomol/L and in healthy males aged 70 to 89 years is 6.4 nanomol/L. Reference ranges using mass spectrometry are less well defined for males aged 35 to 70 years.

Approach to testosterone replacement therapy

Approach to testosterone replacement therapy

Before considering testosterone replacement therapy, perform assessment as outlined in Figure 20.14 to determine whether criteria for a diagnosis of male androgen deficiency are met.

If criteria are not met but functionally low serum testosterone concentration is suspected, consider whether correction of underlying causes is possible. Management should focus initially on lifestyle measures, particularly weight loss where relevant, and treating comorbidities. Australian management guidelines recommend against testosterone therapy for functionally low serum testosterone concentration. The T-Trials [Note 6] enrolled males with functionally low serum testosterone concentrations and at least one of the following problems: decreased libido, difficulty walking, or low vitality. Testosterone treatment modestly

improved sexual function in those with low libido, walking distance in men with difficulty walking, haemoglobin concentration, and lumbar spine bone mineral density, but questions remain about cardiovascular safety, and long-term clinical outcomes.

Consider referral to an endocrinologist for management of functionally low serum testosterone concentration.

If criteria for diagnosing androgen deficiency are met, investigate causes as outlined in Figure 20.14, if feasible, or refer for investigation and management.
The pathological basis of androgen deficiency should be fully investigated before starting testosterone replacement therapy.

Testosterone replacement aims to relieve the symptoms and signs of androgen deficiency. It is not indicated for treatment of low libido or erectile dysfunction in males who are not androgen deficient. The Pharmaceutical Benefits Scheme criteria for prescribing of testosterone for androgen deficiency are stringent; specialist referral is required. Testosterone replacement suppresses spermatogenesis, so referral to a fertility specialist may be required before starting replacement.

Consider referral to discuss fertility options before starting testosterone replacement therapy.

Androgen deficiency may recover if a reversible cause is treated (eg hyperprolactinaemia is corrected with a dopamine agonist). Androgen deficiency caused by an irreversible disorder requires lifelong testosterone replacement therapy.

Testosterone therapy is contraindicated in males with current prostate or breast cancer, those desiring fertility, and elite athletes (because it is a prohibited substance). For males who have had curative treatment for breast or prostate cancer, specialist assessment of harms and benefits of testosterone therapy is required.

Monitoring of testosterone replacement therapy is advised to assess efficacy and detect adverse effects.

Note 6: Snyder PJ, Bhasin S, Cunningham GR, Matsumoto AM, Stephens-Shields AJ, Cauley JA, et al. Effects of testosterone treatment in older men. N Engl J Med 2016;374(7):611-24. [URL]

Testosterone formulations for replacement therapy

Testosterone formulations for replacement therapy

Overview of testosterone formulations

Overview of testosterone formulations

Testosterone replacement therapy for male androgen deficiency can be undertaken with transdermal, injectable or oral testosterone formulations. The choice of formulation is guided by effectiveness, patient preference, convenience and adverse effects.

Transdermal formulations of testosterone may be preferred over intramuscular formulations if the man wishes to avoid injections, has a bleeding disorder or is taking anticoagulants.

Testosterone injections may be more convenient than daily application of transdermal formulations.

Oral testosterone therapy is less effective than other formulations and is rarely used.

Transdermal testosterone replacement therapy

Transdermal testosterone replacement therapy

For transdermal testosterone replacement therapy, use:

1 testosterone 5% cream 2 mL (100 mg) transdermally, in the morning applied to the trunk or proximally on the limbs. Adjust in 1 mL (50 mg) increments according to clinical response and serum testosterone concentration. Maximum dose 4 mL (200 mg) daily *male androgen deficiency, topical therapy*

OR

1 testosterone 1% gel 5 g (50 mg) transdermally, in the morning applied to the trunk or proximally on the limbs. Adjust in 2.5 g (25 mg) increments according to clinical response and serum testosterone concentration. Maximum dose 10 g (100 mg) daily [Note 7]

OR

1 testosterone 2% gel 1 pump (23 mg/1.15 g) transdermally, in the morning applied to trunk or proximally on the limbs. Adjust in 1 pump (23 mg) increments according to clinical response and serum testosterone concentration. Maximum dose 3 pumps (69 mg/3.45 g) daily

OR

2 testosterone patch 5 mg per 24 hours transdermally, at night applied to the trunk or proximally on the limbs for 24 hours. Adjust in 2.5 mg per 24 hours increments according to clinical response and serum testosterone concentration. Maximum dose 7.5 mg per 24 hours.

See Monitoring testosterone replacement therapy for guidance on adjusting testosterone therapy.

The main limitation of transdermal testosterone patches is skin irritation, which is occurs in about 50% of patients and can be severe. Pretreating the application site with topical hydrocortisone may reduce irritation.

To avoid transferring active drug to another person through skin-to-skin contact, advise thorough hand washing after applying testosterone gel or liquid, covering the application area with clothing, and showering before direct skin contact with others. Repeated inadvertent transfer to another person could increase their serum testosterone concentration and cause adverse effects (eg growth of facial or body hair, deepening of the voice, menstrual irregularities in females, premature puberty and genital enlargement in children).

Note 7: Testosterone 1% gel is available in 25 mg and 50 mg sachets, and in a pump dispensing 12.5 mg per actuation.

Intramuscular testosterone replacement therapy

Intramuscular testosterone replacement therapy

Testosterone injection must be given by deep intramuscular injection; it is not recommended in individuals with bleeding disorders or those receiving anticoagulation. Give the injection very slowly to minimise discomfort, and take care to avoid inadvertent intravenous administration.

For intramuscular testosterone replacement therapy, use:

1 testosterone undecanoate 1000 mg by deep intramuscular injection; repeat after 6 weeks and then every 10 to 14 weeks, according to clinical response and serum testosterone concentration. For more gradual replacement, give the second dose after 10 to 14 weeks *male androgen deficiency, intramuscular therapy*

OR

2 testosterone enantate 250 mg by deep intramuscular injection, every 2 to 3 weeks

OR

2 testosterone esters 250 mg by deep intramuscular injection, every 2 to 3 weeks.

See Monitoring testosterone replacement therapy for guidance on adjusting testosterone therapy.

Although uncommon, coughing, dyspnoea, sweating, chest pain, dizziness, paraesthesia, or syncope can occur during or immediately after injection of testosterone. This has been attributed to pulmonary oil microembolism. Treatment is supportive, and further therapy with intramuscular testosterone is not contraindicated.

Testosterone enantate or testosterone ester injections may be associated with marked fluctuation in testosterone concentration, leading to variation in energy, wellbeing and libido.

Oral testosterone replacement therapy

Oral testosterone replacement therapy

Oral testosterone undecanoate is less effective than other testosterone formulations. It has low (under 10%) and variable bioavailability and a short duration of action, so multiple daily doses are required.

For oral testosterone replacement therapy, use:

testosterone undecanoate 120 to 160 mg orally, daily in 2 divided doses for 2 to 3 weeks. Adjust dose according to clinical response and serum testosterone concentration (usual range 80 mg to 240 mg daily). *male androgen deficiency, oral therapy* _

See Monitoring testosterone replacement therapy for guidance on adjusting testosterone therapy.

Monitoring testosterone replacement therapy

Monitoring testosterone replacement therapy

Overview of monitoring testosterone replacement therapy

Overview of monitoring testosterone replacement therapy

Monitoring testosterone replacement therapy for male androgen deficiency involves reviewing response to therapy (by assessing clinical response and measuring testosterone concentration) and being alert to evidence of adverse events. See Table 20.34 for a summary of monitoring undertaken by a specialist or under specialist guidance.

Table 20.34 Monitoring for clinical response and serious adverse effects of testosterone replacement therapy

Reason for monitoring	Action
	review improvement in symptoms of male androgen deficiency 3 months after starting testosterone, then at least annually
assessing adequacy of testosterone replacement	measure serum testosterone concentration 3 to 6 months after starting testosterone, then as determined by response
	measure bone mineral density 12 months or more after starting testosterone
risk of polycythaemia	review FBE at baseline, 3 months after starting testosterone, then at least annually
	assess baseline risk of prostate cancer
risk of promoting growth in a pre-existing prostate cancer [NB1]	exclude symptoms of prostate cancer
	discuss limitations of PSA screening with asymptomatic men; if PSA screening is chosen, see here for advice on frequency of monitoring
cardiovascular risk in frail older men [NB2]	assess baseline cardiovascular risk factors; review for symptoms of fluid overload

Reason for monitoring	Action

- FBE = full blood examination; PSA = prostate specific antigen
- NB1: For discussion of testosterone replacement therapy and prostate cancer risk, see Monitoring for adverse effects of testosterone replacement therapy.
- NB2: Data on cardiovascular risks of testosterone replacement therapy are conflicting; see Monitoring for adverse effects of testosterone replacement therapy.

Monitoring response to testosterone replacement therapy

Monitoring response to testosterone replacement therapy

Most **symptoms and signs** of androgen deficiency respond within 1 to 2 months of starting treatment. Libido is expected to increase; this may be experienced as either a benefit or an adverse effect by men or their partners. Changes in body composition can occur within 3 to 6 months. Assess bone mineral density every 12 months or more to check that the testosterone dose is adequate for bone maintenance.

Measure **serum total testosterone concentration** 3 to 6 months after starting testosterone, then at intervals determined by clinical response and whether dose modification has been required. If testing is required after a change in dose, it should be performed after at least 2 weeks. Target total testosterone concentrations are in the lower half of the reference range. Timing of measurements depends on the testosterone formulation used:

- for **cream**, measure in the morning predose
- for **1% transdermal gel**, measure in the morning predose
- for **2% transdermal gel**, measure 2 to 4 hours after dose
- for **patches**, measure 3 to 12 hours after application
- for **intramuscular testosterone undecanoate**, measure in the morning just before the third dose after a dose change
- for **short-acting injectable formulations** (testosterone enantate and esters), measure in the morning midway between injections.

Multiple-daily dosing with oral testosterone is not readily monitored with serum testosterone concentrations.

Monitoring for adverse effects of testosterone replacement therapy

Monitoring for adverse effects of testosterone replacement therapy

Adverse testosterone effects include common effects (which can be mild and reversible) or more serious effects, for which monitoring is needed. Table 20.34 includes a summary of monitoring for adverse events.

Common adverse effects from testosterone replacement therapy include truncal seborrhoea and acne (particularly with testosterone ester injections), modest weight gain (under 3 kg) and reduced spermatogenesis. Increased truncal hair, temporal hair loss or balding, and gynaecomastia can also occur. Adverse effects generally reverse when therapy is stopped.

Serious adverse effects from testosterone replacement therapy are uncommon but include polycythaemia, prostate growth, and transient worsening of obstructive sleep apnoea. Risk of cardiovascular events and venous thromboembolism may be increased in men taking testosterone, but evidence to confirm this association is lacking.

Polycythaemia occurs most often with short-acting injectable testosterone (esters and enantate forms). Measure haemoglobin and haematocrit at baseline, then 3 months after starting therapy, then annually. Exclude other causes of secondary polycythaemia (including smoking, obstructive sleep apnoea, and respiratory failure). Polycythaemia is treated by interrupting therapy, dose reduction or increasing the dose interval. Occasionally, venesection is required.

Testosterone therapy reverses the reduced prostate volume and prostate specific antigen (PSA) concentration that occur in male androgen deficiency. This **prostate growth** can lead to elevated prostate specific antigen

(PSA), which, if monitored, may prompt investigation for prostate cancer. There is no association between testosterone replacement and incident prostate cancer, except that men with lifelong untreated androgen deficiency are at reduced risk.

For individuals at substantial risk of pre-existing prostate cancer, measure PSA before starting testosterone therapy. If warranted by symptoms, perform digital rectal examination, or refer for urological assessment. Prostate cancer risk may be increased if any of the following are present:

- prostatic symptoms
- a strong family history [Note 8]
- previous serum PSA concentration more than 4 nanogram/mL.

For asymptomatic men, PSA testing before or during testosterone replacement constitutes prostate cancer screening. Given there is no consensus about population screening for prostate cancer, this issue should be addressed by the testosterone prescriber according to existing guidelines, which support discussing screening in males aged 50 to 69 years at average risk using a decision aid [Note 9].

If prostate screening and monitoring is chosen, at the time of writing, guidelines suggest measuring PSA at baseline, then 3 to 12 months after starting testosterone therapy, then every 2 years.

Risk of **cardiovascular events** may be increased in frail older men taking testosterone, although the evidence for an effect of testosterone is mixed and the association is unconfirmed. The T-Trials cardiovascular trial [Note 10] observed a greater 12-month increase in the primary endpoint, noncalcified coronary plaque volume, in testosterone-treated males, but the clinical relevance of this remains undefined. Assess cardiovascular risk before starting testosterone therapy and manage risk factors as for the general population. Closely monitor older people (particularly those with frailty) and those with cardiovascular disease, kidney failure or severe hypertension. Testosterone therapy can cause fluid overload from sodium and fluid retention, which can exacerbate these conditions.

Note 8: For advice on familial prostate cancer risk, see the Royal Australian College of General Practitioners (RACGP) guideline Genomics in general practice.

Note 9: See the Royal Australian College of General Practitioners (RACGP) guideline on prostate cancer screening.

Note 10: Budoff MJ, Ellenberg SS, Lewis CE, Mohler ER, 3rd, Wenger NK, Bhasin S, et al. Testosterone treatment and coronary artery plaque volume in older males with low testosterone. JAMA 2017;317(7):708-16. [URL]

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Definition and causes of delayed puberty in females

Definition and causes of delayed puberty in females

Delayed puberty in females is defined as the absence of breast development by age 13 years, or lack of menarche by age 15 years despite breast development. Acne, body odour and body hair in the absence of breast development may be due to adrenarche (normal adrenal gland hormonal production).

Delayed puberty in females requires specialist referral; it may be caused by:

- constitutional delay (ie delay in completing spontaneous puberty—a normal variant often associated with a family history of delayed puberty) accounting for 30% of cases
- hypothalamic causes, such as functional hypothalamic amenorrhoea (due to conditions such as stress, excessive exercise, systemic illness, or poor nutrition) accounting for 20% of cases, or rare conditions such as Kallmann syndrome [Note 1]
- hypopituitarism
- primary ovarian disorders, such as Turner syndrome.

All females with delayed puberty require referral to a specialist for exclusion or management of underlying causes and pubertal induction, if required.

If there is no evidence of an underlying cause of delayed puberty after initial specialist assessment, treatment may be started by the specialist after an appropriate period of observation. The benefits of inducing puberty in females (eg breast development, growth of genital tract [including uterus], psychosexual development) must be balanced against the potential harm of reducing final height if treatment is started too early.

Note 1: For information on Kallmann syndrome, see the US National Library of Medicine Medline Plus website.

Management of delayed puberty in females

Management of delayed puberty in females

The goal of pubertal induction is to replicate endogenous hormonal production as much as possible. Initial treatment is estrogen only, with progestogen added later (because it can impair normal breast development). Estrogen therapy starts with a very low dose, which is increased slowly over 2 to 3 years to a standard adult replacement dose. Transdermal or oral formulations may be used; transdermal is most common and is preferred, particularly if adverse effects such as thrombotic risks are increased. Progestogen is added once a medium dose of estrogen has been reached, and good glandular development is present in the breasts (which may take up to 2 years), along with vaginal secretion and the start of vaginal bleeding.

If no cause of permanent pubertal failure has been diagnosed, it is reasonable to trial a withdrawal of treatment after 2 years to assess:

- endogenous hormonal status
- whether spontaneous periods occur.

If permanent pubertal failure is confirmed, ongoing hormone replacement therapy with estrogen and progestogen is appropriate, under specialist guidance.

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Introduction to infertility

Introduction to infertility

Infertility is defined as an inability to conceive after 12 months of unprotected regular sexual intercourse. It does not include conditions causing pregnancy loss. The prevalence of infertility is unclear but may range from 10 to 20% of couples trying for a spontaneous pregnancy.

Fertility may be relevant to all individuals, regardless of gender identity. In this topic, female is used to mean anyone presumed female at birth, and male is used to mean anyone presumed male at birth.

A major factor in infertility is increasing age. A female in her mid-twenties has a 25 to 40% likelihood of conceiving each month. This reduces from her early thirties; by age 40 years, the likelihood is only 5% per month. Male fertility declines from age 40 to 45 years.

General practitioners have a key role in education about pregnancy planning to avoid age-related infertility. Consider also referral indications for specialist fertility preservation.

Education about pregnancy planning is key to avoiding age-related infertility.

Lifestyle modifications for promoting fertility

Lifestyle modifications for promoting fertility

Overview of lifestyle modifications for promoting fertility

Overview of lifestyle modifications for promoting fertility

Addressing lifestyle factors can optimise fertility and, in some situations, restore it, avoiding the need for infertility referrals. The website Your Fertility provides evidence-based patient and health professional information sheets about preconception planning.

Lifestyle modification and counselling includes:

- optimising nutrition
- appropriate body weight and exercise
- avoiding tobacco and recreational drugs and minimising alcohol intake
- discussing the normal fertile period and timing of sexual activity.

Nutritional supplements and fertility

Nutritional supplements and fertility

Both folate and iodine are required as supplements for all females planning pregnancy. Their major benefit is promoting normal development of the brain and spinal cord, but they may also benefit fertility (although this is not certain). Advise folate supplementation for all females for at least 1 month before and for the first 3 months of pregnancy, to minimise the risk of neural tube disorders. Iodine supplementation (150 micrograms daily) is also advised for all females before and during pregnancy. Uncertain fertility benefit has also been suggested for:

- vitamin D supplementation in females and males who are deficient
- increasing dietary zinc and selenium intake in males; see here for guidance on dietary sources.

Weight management to optimise fertility

Weight management to optimise fertility

In males and females, fertility is impaired if body mass index (BMI) is too low or too high. Consider underlying causes of abnormal weight, including eating disorders, before starting fertility treatments. For those who are overweight or obese, see General principles of managing excess body weight. Before considering pharmacotherapy to induce ovulation, consider the need for weight loss. A 5% reduction in body weight in overweight or obese anovulatory females may improve response to ovulation induction and reduce the risk of gestational diabetes.

For overweight or obese females, losing 5% of body weight can improve fertility and reduce the risk of gestational diabetes.

Rapid weight loss is not desirable because it may have effects on the fetus; females should wait at least 1 year after bariatric surgery before trying to conceive. The safety of weight loss medications (such as phentermine or liraglutide) in pregnancy is unknown; their use is not recommended in females planning pregnancy. The impact of bariatric surgery on male fertility is not clear; studies have conflicting results.

The BMI threshold for fertility treatment in females is controversial. Several authorities suggest BMI should be below 35 kg/m^2 before treatment, including assisted reproductive technology; however, the female's age and time remaining for fertility treatment should be considered.

Advice on tobacco, alcohol and recreational drugs for fertility

Advice on tobacco, alcohol and recreational drugs for fertility

There are no safe limits for smoking, alcohol consumption or recreational drug use in relation to fertility in males or females. Offer help with behavioural change; see the Royal Australian College of General Practitioners (RACGP) guide on Smoking, nutrition, alcohol, physical activity . Patient resources are also available on the Your Fertility website.

Advice on ovulation prediction to determine the fertile window

Advice on ovulation prediction to determine the fertile window

Ovulation prediction can help determine the fertile window (the days on which conception is possible); this lasts from 5 days before ovulation until the day it occurs, as sperm survive in the female reproductive tract for this duration. Intercourse every 2 to 3 days is adequate during this time period to achieve pregnancy.

In discussing the normal fertile window, provide advice about how to predict ovulation. No single method of ovulation prediction is ideal; options include:

- calculating the day of ovulation from historical menstrual cycle data (if cycles are regular): ovulation is expected about 14 days before the last day of the cycle (eg for a 30-day cycle, ovulation is expected on day 16)
- measuring basal body temperature: detecting the 0.2 to 0.5°C rise in body temperature that occurs following ovulation
- assessing cervical mucus: texture becomes slippery several days before ovulation; see the Billings Ovulation Method
- measuring urinary luteinising hormone (LH) concentration: the most useful adjunct to menstrual cycle data; this detects an LH surge about 20 hours before ovulation.

Testing salivary composition is not reliable for ovulation prediction.

Fertility applications (apps) predict ovulation using historical menstrual cycle data, sometimes in combination with one or more other parameters. Apps are popular but generally unreliable, particularly those using historical cycle data alone.

Ensuring comprehensive preconception care in fertility consultations

Ensuring comprehensive preconception care in fertility consultations

A comprehensive clinician guide to preconception care is available in the Royal Australian College of General Practitioners (RACGP) guidelines on Preventive activities prior to pregnancy. These aspects of care should be covered in all consultations with prospective parents. In those with fertility concerns, time may be scarce; arrange preconception investigations in parallel with referral to a fertility specialist to avoid delays if referral is urgent.

Ensure comprehensive preconception investigations are arranged when referring for infertility assessment.

Advice about genetic risk and fertility

Advice about genetic risk and fertility

Assessing personal and family history features for risk to fertility

Assessing personal and family history features for risk to fertility

Some individuals have a personal or family history that suggests risk to fertility. Recurrent miscarriage, stillbirth, developmental disability or congenital anomalies, for example, may indicate genetic causes that can affect fertility or health of offspring. See the section on Family history in the Royal Australian College of General Practice (RACGP) guideline *Genomics in General Practice*. Consider referral to or seeking advice from a genetic service; see the Centre for Genetics Education website for a state-based directory of genetic services. Concurrent referral to an infertility specialist may be appropriate if time is scarce.

Reproductive carrier screening and preconception care

Reproductive carrier screening and preconception care

All prospective parents (regardless of fertility concerns) should be made aware of reproductive carrier screening. These tests aim to detect genetic risks to offspring that are unlikely to be apparent on history taking; the results of some tests can also affect the prospective parents' fertility and management options. See the RACGP guidance on reproductive carrier screening for more information.

Limited reproductive carrier testing offers preconception testing to both partners for thalassaemia, spinal muscular atrophy, cystic fibrosis and fragile X. More extensive carrier screening for a broad range of conditions is available, and may become more popular as costs diminish and their utility is better established.

See the Centre for Genetics Education website for information on:

- access to genetic services
- reproductive carrier testing of prospective parents
- embryo testing before implantation during in-vitro fertilisation to prevent inheritance of some genetic disorders
- prenatal testing of fetal DNA during pregnancy.

Consider genetic risk assessment and management for all prospective parents.

Causes of infertility

Causes of infertility

Human reproduction depends on fertility (the ability to conceive) and the capacity to maintain a fetus *in utero*. It requires:

- production of gametes (sperm and oocytes) capable of fertilisation
- release of the oocyte into a patent fallopian tube after ovulation
- timely deposition and migration of sufficient fertile sperm in the female reproductive tract to enable fertilisation
- implantation and development of the embryo in the hormonally primed uterine mucosa
- maintenance of the growing fetus in the uterus until it is fully viable.

Infertility may be due to factors in the female partner (in about 40% of couples), the male partner (in about 40% of couples), both partners or unexplained factors.

In females, causes of impaired fertility include:

- anovulation from a range of causes, most commonly polycystic ovarian syndrome
- endometriosis causing tubal obstruction, changes to endometrial function and reduced sexual activity due to pain
- tubal obstruction and uterine anomalies.

In males, causes of impaired fertility include:

- failed spermatogenesis (which may be primary [testicular] or central [pituitary or hypothalamic])
- reduced numbers or motility, or changed morphology of the sperm

- failed delivery of sperm, due to obstruction of the vas deferens (as occurs in congenital bilateral absence of the vas deferens in cystic fibrosis), or a testicular tumour, or erectile or ejaculatory failure).

Assessment of infertility

Assessment of infertility

History and examination in infertility

History and examination in infertility

In addition to taking a general medical, surgical and family history for both partners, assess factors specific to female fertility and male fertility. Also assess factors affecting sexual activity.

In assessing **female factors**, determine whether the individual has:

- irregular cycles (less than 24 days or longer than 38 days) or oligomenorrhoea (fewer than 9 cycles in 1 year), which can suggest polycystic ovarian syndrome (PCOS)
- amenorrhoea (absent bleeding for more than 3 months for a female with regular cycles, or more than 6 months for a female with irregular cycles), which can suggest:
  - functional hypothalamic amenorrhoea (caused by conditions such as stress, excessive exercise, systemic illness, eating disorders and very low body weight)
  - pituitary disorders (including prolactinoma and premature ovarian insufficiency or premature menopause)
  - other endocrine causes of secondary amenorrhoea, which are rarer
- symptoms of endometriosis (eg dysmenorrhoea, spotting, deep dyspareunia)
- other factors likely to block the fallopian tubes, such as previous pelvic inflammatory disease or surgery.

In assessing **male factors**, determine whether the individual has:

- testicular problems (eg cryptorchidism, injury, torsion, hernia, mumps orchitis, varicocele)
- symptoms of androgen deficiency
- exogenous anabolic steroid use
- difficulties with erections and ejaculation.

In assessing the timing and frequency of **sexual activity**:

- ask what the couple understand about the fertile window
- establish the frequency of sexual activity and whether symptoms of sexual difficulties, such as altered libido, pain or erectile or ejaculatory difficulties, are present.

A full **physical examination** of both partners should include body mass index (BMI), signs of normal secondary sexual characteristics and, if indicated, pelvic examination. See Examination of the vulva and vagina and Examination of the penis and testes for advice on reducing distress related to examination. Examine for signs of PCOS, including acne and hirsutism; note that weight is not always increased. Pelvic examination may detect tenderness suggestive of endometriosis or pelvic inflammatory disease. Testicular examination looks for small volume and lack of virilisation (which could indicate Klinefelter syndrome [Note 1]), masses (eg tumours, hernias, varicoceles) or palpable absence of the vas deferens (which may be a sign of cystic fibrosis).

Note 1: For information on Klinefelter syndrome, see the US National Library of Medicine Medline Plus website .

Laboratory and radiological investigations in infertility

Laboratory and radiological investigations in infertility

See Table 20.24 for a guide to laboratory investigations of infertility that are helpful in general practice.

Radiological investigation can be requested in general practice. Transvaginal ultrasound scan of the ovaries, tubes and uterus is useful for all females with suspected infertility, and should be performed in the first half of the menstrual cycle [Note 2]. It can estimate the number of follicles as well as abnormal anatomy of the uterus. If PCOS is suspected, specifically request evaluation for an abnormally high follicle count.

Serum anti-Mullerian hormone (AMH) testing in females is not advised, except in a specialist setting. It is an indicator of the number of ovarian follicles remaining but not of the quality of oocytes, so is not a straightforward predictor of fertility. In males, testing of antisperm antibodies is not recommended in general practice, because evidence of their impact on fertility is insufficient.

Testing of serum anti-Mullerian hormone should be reserved for a specialist setting.

Tests of tubal patency (eg hysterosalpingogram, hysteroscopic contrast sonography [HyCoSy], laparoscopy with dye) should be reserved for request by a specialist or a general practitioner with experience in fertility treatments, with imaging performed in centres with specialist interest in these tests.

In males, additional tests that may be considered by specialists include a karyotype, testing for Y chromosome aberrations, haemochromatosis and serum sex hormone–binding globulin concentration.

Table 20.24 Laboratory investigations of infertility

Printable Table

tests in females

- serum FSH, LH, prolactin and estradiol
- serum testosterone and SHBG
- serum hCG
- serum TSH
- serum progesterone
- test for chlamydia and gonorrhoea

tests in males

- semen analysis
- serum FSH and prolactin, and morning fasting serum testosterone and LH

- test for chlamydia and gonorrhoea

Tests in females (may be abnormal if recent illness)	
Test serum FSH, LH, prolactin and estradiol	
Reason for test	to distinguish hypothalamic or pituitary causes of anovulation from ovarian causes
Timing of sample collection	preferably in the first week of a cycle [NB1]
Indications to test	irregular or absent menstrual cycles
Test serum testosterone and SHBG	
Reason for test	to detect elevated serum testosterone and reduced SHBG in PCOS assessment
Timing of sample collection	preferably in the first week of a cycle [NB1]
Indications to test	if PCOS is suspected
Test serum hCG	
Reason for test	to exclude pregnancy as a cause for anovulation
Timing of sample collection	any time
Indications to test	unexplained amenorrhoea
Test serum TSH	
Reason for test	to detect hypothyroidism or hyperthyroidism causing anovulation
Timing of sample collection	any time
Indications to test	irregular or absent menstrual cycles
Test serum progesterone	
Reason for test	to detect a rise in progesterone to indicate ovulation
Timing of sample collection	one week before anticipated period (ie day 21 of a 28 day cycle)
Indications to test	all females
Test for chlamydia and gonorrhoea	
Reason for test	as part of a screen for STIs
Timing of sample collection	any time
Indications to test	all females
Tests in males (may be abnormal if recent illness)	
Test semen analysis [NB2]	
Reason for test	to assess numbers, morphology and motility of sperm
Timing of sample collection	after 2 to 5 days abstinence (retest if first test is abnormal)
Indications to test	all males
Test serum FSH and prolactin, and **morning fasting** serum testosterone and LH	
Reason for test	to distinguish hypothalamic or pituitary causes from primary testicular conditions
Timing of sample collection	any time
Indications to test	if semen analysis abnormal
Test for chlamydia and gonorrhoea	
Reason for test	to investigate symptoms or signs of an STI
Timing of sample collection	any time
Indications to test	males with symptoms or signs (eg discharge, dysuria, scrotal pain) or raised leucocyte count in sperm, or those at risk of an STI

FSH = follicle stimulating hormone; hCG = human chorionic gonadotrophin; LH = luteinising hormone; PCOS = polycystic ovary syndrome; SHBG = sex hormone–binding globulin; STI = sexually transmitted infection; TSH = thyroid stimulating hormone.

NB1: If a female is not cycling, testing can be undertaken on any convenient day and referral for assessment by a fertility specialist should not be delayed by waiting for a menstrual period.

NB2: See the 'Male Infertility' clinical summary guide on the Healthy Male website for normal parameters for semen analysis. Testing sperm autoantibodies is not recommended in general practice.

Note 2: A transvaginal ultrasound scan is preferred because it is gives best detail, including more reliable follicle counts. A transabdominal approach is an alternative if a transvaginal scan is not available or is declined. In amenorrhoea, ultrasound can be undertaken as soon as is convenient and referral to a fertility specialist should not be delayed by waiting for a menstrual period.

When to refer for fertility treatment and preservation

When to refer for fertility treatment and preservation

Because fertility in all people declines naturally with age, refer for expert advice if conception has not occurred after trying for:

- 1 year if the female is 35 years or younger
- 6 months if the female is older than 35 years (because treatment success diminishes with age).

Earlier referral is indicated if known causes of or predisposing factors to infertility exist.

Consider referral for fertility preservation in situations such as:

- before treatment for some cancers
- before gender-affirmation treatment; see the TransHub website for information on fertility in transgender and gender diverse people
- for social reasons.

Units accredited for fertility treatment and preservation in Australia and New Zealand are listed on the Fertility Society website .

Additional support in dealing with the psychological impact of infertility or at-risk fertility may help reduce distress and improve pregnancy outcomes. Offer patients an opportunity to discuss their feelings, and consider referral to a mental health professional.

Anovulatory infertility

Anovulatory infertility

Causes of anovulatory infertility

Causes of anovulatory infertility

In approximately 10 to 20% of infertile couples, infertility is largely due to lack of ovulation. Anovulation is suggested by irregular menstrual cycles (less than 24 days or longer than 38 days) or amenorrhoea (absent bleeding for more than 90 days for a female with regular cycles, or more than 6 months for a female with irregular cycles).

Polycystic ovary syndrome (PCOS) is the most common cause of anovulation; it typically presents with irregular menstrual cycles.

Anovulation presenting with amenorrhoea may be related to:

- functional hypothalamic amenorrhoea (eg due to stress, excessive exercise, systemic illness, eating disorders or very low body weight)
- pituitary disorders (including prolactinoma and premature ovarian insufficiency or premature menopause)
- other endocrine causes of secondary amenorrhoea, which are rarer.

Exclude pregnancy as part of the assessment of anovulation.

The cause of anovulation should be determined before starting ovulation induction; the underlying disorders may have implications for general health, as well as fertility.

Ensure timely referrals for ovulation induction to maximise the likelihood of specialist treatment succeeding.

Anovulation should be thoroughly investigated but timely specialist referral is important for optimal treatment.

Approach to ovulation induction

Approach to ovulation induction

The approach to treating anovulation depends on the cause.

Individuals with premature ovarian insufficiency require prompt referral to a fertility specialist because assisted reproductive technology with a donor oocyte or embryo is generally required.

For individuals with a disorder of the hypothalamic–pituitary axis, first address underlying causes (eg low weight, systemic illness, stressors). Treat hyperprolactinaemia with dopamine agonists.

For individuals with PCOS, address diet and exercise first; also consider metformin (see PCOS and subfertility for more information).

If anovulation persists in individuals with a hypothalamic–pituitary disorder or PCOS, ovulation induction may be useful. This is the process of promoting the release of an oocyte from a single mature ovarian follicle [Note 3]. The oocyte can then be fertilised naturally, or with intrauterine insemination. Drugs to induce ovulation should only be used with specialist guidance or prescribed by a specialist, because there is a risk of multiple follicles developing; see Assessing for multiple follicles in ovulation induction.

Specialist guidance is required for ovulation induction because there is a risk of multiple follicles developing.

Drugs to induce ovulation include aromatase inhibitors (eg letrozole), estrogen receptor antagonists (eg clomifene) and gonadotrophins (follicle stimulating hormone [FSH] with human chorionic gonadotrophin [hCG]). Letrozole and clomifene work by suppressing estrogenic feedback on the hypothalamus, so are unlikely to be effective in females with low serum estradiol. Gonadotrophins are preferred in this situation, or when letrozole and clomifene have been ineffective or cannot be used (eg due to patient concerns about adverse effects).

Note 3: This is a different process to controlled ovarian hyperstimulation, which is used in in-vitro fertilisation to promote the maturation of multiple follicles.

Before starting ovulation induction

Before starting ovulation induction

Before ovulation induction is started, exclude pregnancy and perform standard initial investigations on both partners (including a semen analysis).

Tests performed by specialists (or general practitioners with experience in fertility treatments) to assess fallopian tube patency and uterine anatomy include hysterosalpingogram, hysteroscopic contrast sonography (HyCoSy) and laparoscopy with dye tests. These should be performed:

- before ovulation induction if the female has a history of pelvic infection or surgery
- after 3 to 6 cycles of letrozole or clomifene if the female does not conceive despite confirmed ovulation
- if planning to use FSH.

The timing of ovulation induction by a specialist may depend on the individual's hormonal profile. Induction can be started in those who are amenorrhoeic if they have basal hormones typical of the follicular stage. Some clinicians don't assess basal hormones and instead give a short course of a progestogen to induce uterine bleeding; this may make the endometrium more suitable for implantation later in the cycle. Pretreatment with a progestogen can also be useful to guide the specialist choice of ovulation induction drug. If a bleed does not occur after taking a progestogen, letrozole or clomifene are unlikely to be effective (because serum estradiol is likely too low for the drugs to suppress estrogenic feedback on the hypothalamus), and gonadotrophins are preferred.

A typical progestogen pretreatment regimen is:

1 medroxyprogesterone 10 mg orally, once daily for 10 days *infertility* _

OR

1 norethisterone 5 mg orally, once daily for 10 days. *infertility* _

Letrozole for ovulation induction

Letrozole for ovulation induction

Letrozole is a more effective promoter of ovulation than clomifene; higher pregnancy rates and less frequent multifollicular development are reported. However, letrozole is not registered by the Australian Therapeutic Goods Administration (TGA) for this indication. Although initial reports suggested a higher congenital abnormality rate in children conceived after letrozole therapy, multiple subsequent studies have not shown any difference in abnormality rates compared to clomifene.

Use of letrozole for ovulation induction requires specialist guidance and monitoring; see Assessing response to ovulation induction. A typical regimen is:

letrozole 2.5 to 5 mg orally, once daily for 5 consecutive days. Start between days 2 to 5 of the menstrual cycle. *infertility* _

If ovulation does not occur, an increased dose of letrozole is used for each of the next two cycles before considering other drugs.

Clomifene for ovulation induction

Clomifene for ovulation induction

Clomifene increases endogenous gonadotrophin secretion by blocking negative feedback of estrogen to receptors, particularly on the hypothalamus.

Use of clomifene requires specialist guidance and monitoring; see Assessing response to ovulation induction. A typical regimen is:

clomifene 50 mg orally, once daily for 5 consecutive days. Start between days 2 to 5 of the menstrual cycle. *infertility, ovulation induction* _

If ovulation does not occur, an increased dose of clomifene is used for the next two cycles before considering other oral drugs. Clomifene results in ovulation in 80% of users, but only 40 to 60% become pregnant; the endometrium and cervical secretions may not be as favourable for conception as with letrozole or gonadotrophins.

Blurred or double vision or visual field defects have been reported in 1 to 2% of clomifene users. These usually resolve but treatment should not be continued. Current practice is to limit clomifene use to less than 12 months because there is a possible increased risk of ovarian cancer with long-term use, although evidence for an association is insufficient [Note 4].

Note 4: Rizzuto I, Behrens RF, Smith LA. Risk of ovarian cancer in women treated with ovarian stimulating drugs for infertility. Cochrane Database Syst Rev 2019;6:CD008215. [URL]

Gonadotrophins for ovulation induction

Gonadotrophins for ovulation induction

Ovulation induction with gonadotrophins involves use of:

- FSH, which recruits and matures follicles during the first few days of treatment [Note 5], followed by
- high-dose (5000 to 10 000 units) hCG, which acts like luteinising hormone (LH) to trigger active ovulation of a single dominant mature follicle. This is known as the 'hCG trigger injection' (also used in in-vitro fertilisation).

The main hazards of ovulation induction with gonadotrophins are development of multiple follicles (leading to a multiple pregnancy) and ovarian hyperstimulation syndrome (OHSS) {OHSS in IVF}. Therefore, they should only be used be used with specialist guidance and monitoring.

Note 5: Some females who lack luteinising hormone (LH) (eg as a result of severe hypothalamic or pituitary disorders) may also need a small dose of recombinant LH or a very low dose of human chorionic gonadotrophin (hCG) in the follicular phase.

Assessing response to ovulation induction

Assessing response to ovulation induction
Confirming ovulation after induction

Ovulation is confirmed by measuring the serum progesterone concentration in the midluteal phase (5 to 10 days before the start of menstruation).

If ovulation does not occur, usual practice is to increase the daily dose of letrozole or clomifene for each of the next two cycles, before considering gonadotrophins.

If ovulation is confirmed, but pregnancy fails to occur after three to six cycles of treatment with letrozole or clomifene, other causes of infertility should be excluded before further treatment is considered. Assessment includes tests of fallopian tube patency and uterine imaging (eg hysterosalpingogram, hysteroscopic contrast sonography [HyCoSy]) and laparoscopy with dye tests.

Assessing for multiple follicles in ovulation induction

All individuals taking drugs to induce ovulation must be monitored by an experienced clinician because there is a risk of multiple follicles developing. Multiple follicles may develop into a multiple pregnancy (in a few percent of conceptions) or cause ovarian hyperstimulation syndrome (OHSS). These risks are slightly increased with clomifene and letrozole, but are substantial with gonadotrophins.

All individuals taking drugs to induce ovulation must have monitoring to detect multiple follicles and manage risks.

OHSS is rare with ovulation induction, and is more likely with in-vitro fertilisation (IVF). Individuals may present directly to their general practitioner with symptoms of OHSS. The severity is very variable, but OHSS can be life-threatening, so it is important to be aware of the features and approach to assessment of OHSS.

Monitoring for multiple follicles involves ultrasound investigations and laboratory tests (including serum estrogen concentrations). If multiple follicles do develop, adverse effects may be avoided by cancelling the treatment cycle, avoiding unprotected intercourse and not giving an ovulation trigger (eg high-dose hCG).

Polycystic ovary syndrome and subfertility

Polycystic ovary syndrome and subfertility

Infertility is not absolute in individuals with polycystic ovary syndrome (PCOS). Some ovulate spontaneously, and may conceive without needing ovulation induction; however, time to conception is usually prolonged. In those who are obese or have impaired glucose tolerance, the risk of early miscarriage is increased and pregnancy complications are more frequent (including gestational diabetes, pre-eclampsia and delivery problems).

First-line therapy for infertility in individuals with PCOS is **lifestyle modification,** including diet and exercise. A 5% reduction in body weight in overweight or obese anovulatory individuals may improve fertility and reduce the risk of gestational diabetes. For detailed information, see the lifestyle algorithm in the *PCOS Practice Tools for Health Practitioners*, available from Monash University

Diet and exercise are first-line fertility therapies for overweight or obese individuals with PCOS.

If lifestyle changes do not improve fertility, refer to a specialist experienced in reproductive medicine for consideration of ovulation induction with letrozole, clomifene or gonadotrophins.

Metformin can induce ovulation in individuals with PCOS (it also has other indications in PCOS). It is not as effective as clomifene or letrozole. It is most likely to benefit individuals with a body mass index over 30 kg/m^2. Measurement of insulin resistance does not predict who will respond to metformin for ovulation induction. Metformin can be considered:

- while awaiting specialist referral
- if other drugs (clomifene, letrozole, gonadotrophins) are contraindicated
- if monitoring for other drugs is not available
- if the individual is not in a hurry to conceive (more effective drugs are preferred).

Metformin can be trialled alone for up to 1 year; consider clinical review after 3 months. See Metformin for individuals with PCOS for dose recommendations.

Individuals with PCOS have an unpredictable response to **letrozole, clomifene and gonadotrophins**, and are more likely to develop multiple follicles than females with other anovulatory conditions; response may vary from one cycle to the next. Risks of a multiple pregnancy or OHSS are increased.
Ovulation induction with letrozole, clomifene or gonadotrophins for females with PCOS requires specialist referral; risks are greater than for females with other anovulatory conditions.

Combination therapy with clomifene and metformin may improve pregnancy rates in individuals with PCOS who do not respond to clomifene alone. The effect of combining metformin and letrozole is not known.

If letrozole or clomifene treatment does not achieve ovulation, gonadotrophins can be used.

If other therapies have not been effective, options include:

- **laparoscopic ovarian drilling**—this involves diathermy or laser to create punctures in the ovary, which are thought to disrupt follicles and possibly improve ovulation by reducing androgens and inhibins
- in-vitro fertilisation —particularly if the partner is also infertile. Strategies are required to reduce the risk of OHSS and a single embryo is transferred to avoid multiple pregnancies.

Endometriosis-related infertility

Endometriosis-related infertility

Endometriosis can cause infertility by producing adhesions around fallopian tubes and ovaries, and endometriomas in the ovaries. It may also interfere with fertilisation or implantation of embryos, although there is less evidence for this. Endometriosis can cause deep dyspareunia, which may reduce the frequency of intercourse.

Laparoscopic surgery is preferred to drug therapy for infertility caused by endometriosis. Surgery requires specific expertise in endometriosis management, because it may involve extensive excision and ablation of endometriotic deposits and dividing adhesions. Deposits on the ovary should not be excised because there is a risk of depleting oocytes.

In-vitro fertilisation (IVF) may be required if significant tubal obstruction remains after surgery. Success rates are slightly lower than in other conditions treated with IVF.

For information on the management of endometriosis, see Approach to treating endometriosis. Hormonal therapies used to treat other aspects of endometriosis may interfere with conception and are not suitable for females trying to conceive.

Infertility related to other tubal and uterine anomalies

Infertility related to other tubal and uterine anomalies

Absolute fallopian tubal blockage is an indication for in-vitro fertilisation (IVF) because tubal unblocking and surgery are rarely successful. The presence of hydrosalpinges seen on ultrasound is an indication for salpingectomy because fluid from diseased tubes may affect a replaced embryo. Reversal of tubal ligation only results in a live birth in about 50% of cases, but success rates fall in those older than 40 years; assisted reproductive technology (ART) may be required.

Intrauterine adhesions (detected by hysteroscopy) can affect fertility. Although rare, they may occur following dilatation and curettage, miscarriage, or extrapulmonary tuberculosis. The extent of adhesions predicts the outcomes of fertility treatment; severe intrauterine scarring (severe Asherman syndrome) has a particularly poor outcome. Hysteroscopic removal of adhesions has variable outcomes.

Subserosal fibroids are not thought to cause infertility, but submucous fibroids or those impacting the endometrium should be evaluated by a specialist; myomectomy may be required.

Male infertility

Male infertility

Approach to male infertility treatment

Approach to male infertility treatment

Most males seeking treatment for infertility (85 to 90%) require assisted reproductive technology (ART), because sperm number or quality is too low to achieve unassisted conception. Sperm may be collected from semen, but in some cases testicular biopsy is necessary or donated sperm is required. ART is the treatment of choice for individuals with abnormal semen analysis of unknown cause. A range of other therapies has been tried but none consistently improves fertility, so they are not recommended. These include hormones and hormone antagonists (gonadotrophins, antiestrogens), nutritional supplements, anti-inflammatory drugs, antibiotics and physical therapies (testicular cooling).

ART is also the treatment of choice for infertility after vasectomy reversal. Factors affecting the decision to use ART following reversal include time since reversal, intraoperative findings and partner age.

Gonadotrophin therapy can induce spermatogenesis and fertility in some males with hypogonadotrophic hypogonadism. If this is not successful, ART can be offered as second-line treatment.

Individuals with erectile dysfunction need investigation for underlying medical conditions before starting treatment.

Gonadotrophin therapy for male infertility

Gonadotrophin therapy for male infertility

Gonadotrophin therapy is used by specialists in males with hypogonadotrophic hypogonadism to induce spermatogenesis and fertility. Before starting gonadotrophin treatment, investigate for and manage modifiable causes of hypogonadotrophic hypogonadism, including:

- pituitary tumours
- hyperprolactinaemia
- syndromes associated with iron overload (eg haemochromatosis, thalassaemia)
- use of exogenous testosterone or selective androgen receptor modulators (SARMs), which suppress pituitary function via negative feedback.

Permanent causes of hypogonadotrophic hypogonadism include congenital conditions such as Kallmann syndrome [Note 6].

Testosterone replacement is sometimes used to treat male androgen deficiency in individuals with hypogonadotrophic hypogonadism. However, as testosterone replacement supresses spermatogenesis, it should be deferred until after fertility treatment.

Androgen-deficient males should not receive testosterone supplementation until after fertility treatment.

Treatment with human chorionic gonadotrophin (hCG) alone may improve sperm count in males who have been through spontaneous puberty; however, some males need follicle stimulating hormone (FSH) added after a trial of hCG alone. Predictors of success include an initial testis size of more than 4 mL (measured using an orchidometer) and previous treatment with gonadotrophins.

Before starting gonadotrophins in a male, the partner may be assessed for conditions that could affect treatment success (eg anovulation, tubal obstruction).

Gonadotrophin therapy begins with hCG alone for up to 6 months. A suitable regimen is:

human chorionic gonadotrophin 1500 international units subcutaneously, 2 or 3 times weekly. *male infertility* _

Response to hCG treatment is monitored by:

- trough serum testosterone concentration immediately before an injection, 3 months after starting therapy
- clinical evaluation of sexual function (eg changes in libido, erectile function) and general health
- semen analysis.

If hCG alone does not adequately improve sperm count after an adequate trial (usually 6 months), FSH is added. This is required in many gonadotrophin-deficient infertile males. A suitable regimen is:

1 follitropin alfa 50 to 150 international units subcutaneously, 3 times weekly *male infertility* _

OR

1 follitropin beta 50 to 150 international units subcutaneously, 3 times weekly. *male infertility* _

Treatment with FSH is monitored by semen analysis every 3 months.

If the individual has not gone through spontaneous puberty, normal testis size (more than 15 mL) and normal sperm output are rarely achieved with gonadotrophin therapy. However, pregnancy may be achievable when the sperm count is still low. When the sperm count reaches a measurable concentration, the option of freezing semen for future use should be offered. Even when this sperm concentration is not achieved, gonadotrophin therapy may allow sufficient sperm to be collected (from semen or a testicular biopsy) for intracytoplasmic sperm injection (ICSI).

Note 6: For information on Kallmann syndrome, see the US National Library of Medicine Medline Plus website.

Unexplained infertility

Unexplained infertility

Unexplained infertility is a condition where extensive investigation of both male and female partners does not reveal any abnormalities that would impair fertility. Use of oral ovulation drugs is not warranted; assisted reproductive technology using intrauterine insemination (IUI) or in-vitro fertilisation (IVF) is usually the best option.

Assisted reproductive technology

Assisted reproductive technology

Introduction to assisted reproductive technology

Introduction to assisted reproductive technology

Assisted reproductive technology (ART) is a specialist service used to treat a range of causes of infertility. ART includes intrauterine insemination (IUI), in-vitro fertilisation (IVF) and intracytoplasmic sperm injection (ICSI).

See the Victorian Assisted Reproductive Treatment Authority for patient and health professional resources on fertility treatments, including the use of donor gametes (oocytes or sperm), surrogacy and fertility preservation. Accredited units in Australia and New Zealand are listed at the Fertility Society website.

Intrauterine insemination

Intrauterine insemination

Intrauterine insemination involves washing sperm to remove chemicals in seminal fluid that may otherwise lead to uterine contractions. The washed sperm is placed in the uterus at the time of ovulation.

Intrauterine insemination can be combined with ovulation induction. It can also be used alone in erectile dysfunction, couples where sexual or other difficulties preclude penetrative sexual intercourse, abnormalities of cervical mucus, unexplained infertility, or when donor sperm is used (eg for same-sex couples or people conceiving without a partner). Contraindications are tubal blockages and very poor sperm quality.

In-vitro fertilisation (IVF)

In-vitro fertilisation (IVF)

In-vitro fertilisation (IVF) is an option in a range of infertility conditions and can use a couple's own or donor gametes (oocytes and sperm). Controlled hyperstimulation of the ovaries is required so that multiple follicles mature, in contrast to ovulation induction, in which the goal is to promote maturation of a single follicle.

Gonadotrophins are used in higher doses in IVF compared with ovulation induction. Combinations of gonadotrophins can be used, and gonadotrophins can also be used with other drugs. Treatments used include:

- gonadotrophin-releasing hormone (GnRH) agonists or antagonists, to prevent premature oocyte release
- high-dose human chorionic gonadotrophin (hCG) 'trigger injection', to release the oocytes (given 36 hours before oocyte collection)
- vaginal progestogen or hCG, to support the luteal phase of the menstrual cycle (by ensuring the endometrium is ready for implantation).

After oocytes are matured in the follicles, they are collected by transvaginal fine needle aspiration with ultrasound guidance. Fertilisation is facilitated in the laboratory by putting oocytes and sperm together. Embryos are selected according to morphology; in some situations, testing for chromosomal or genetic anomalies is warranted—see the Victorian Assisted Reproductive Treatment Authority for more information. The embryo(s) resulting from IVF are placed in the uterus via the transvaginal route, usually as a single embryo transfer to minimise the risks of multiple pregnancies.

Intracytoplasmic sperm injection (ICSI) involves IVF with the additional step of injecting each harvested oocyte with a single sperm to overcome problems such as poor sperm motility or very low sperm count. ICSI is used in 60 to 80% of IVF treatments in Australia. The incidence of congenital anomalies is slightly increased with ICSI compared to IVF alone.

Ovarian hyperstimulation syndrome

Ovarian hyperstimulation syndrome

The high doses of gonadotrophins used in IVF or ICSI treatment can result in ovarian hyperstimulation syndrome (OHSS). OHSS is the abnormal release of cytokines from the ovaries, which increases the permeability of blood vessels and causes leakage of fluid from the vasculature into the tissues. OHSS occurs in less than 2% of cycles in IVF and uncommonly in ovulation induction. Gonadotrophin treatment must be monitored by practitioners with experience in recognising OHSS and access to facilities for treating females with OHSS.

OHSS can be a medical emergency; early detection and management is important. Serious complications can occur, such as:

- ascites, pleural or rarely, pericardial effusions
- acute kidney failure
- venous and arterial thrombosis
- cerebral oedema
- ovarian torsion
- ileus
- death.

Ovarian hyperstimulation syndrome can be a medical emergency.

OHSS usually occurs within 7 to 10 days of the hCG trigger injection. Symptoms range from mild abdominal discomfort or bloating, to severe abdominal pain (due to massive ovarian enlargement and ascites), vomiting and dehydration. Seek advice from an ART clinician if OHSS is suspected.

If the individual has mild abdominal discomfort, normal urine output, and no vomiting, diarrhoea, shortness of breath or biochemical evidence of volume depletion, they can be managed in the community (provided they have support at home) with advice from the treating ART clinician. Encourage fluid intake (2 L water daily) and gentle activity (but not strenuous exercise or intercourse), and organise prompt review by the ART clinician. Thromboprophylaxis may be required.

Urgent review by the treating ART clinician or referral to an emergency department is needed if any of the following occur:

- moderate to severe abdominal pain or bloating
- nausea or vomiting
- shortness of breath
- reduced urine output.

Hospital management includes:

- immediate notification of the gynaecologist on call
- investigations including urea, electrolytes, full blood count, coagulation profile
- strict fluid balance and intravenous fluid replacement if significantly volume depleted
- thromboprophylaxis
- analgesia
- antiemetics
- management of complications.

For comprehensive management guidelines, see the South Australian Health Perinatal Practice Guideline on Ovarian hyperstimulation syndrome .

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[X] Close

Diagnosis of endometriosis

Diagnosis of endometriosis

Endometriosis is a chronic inflammatory gynaecological condition caused by hormone-dependent growth of endometrial-like tissue outside the uterus. Deposits grow on the peritoneum and the ovary and may be superficial or infiltrating. Those that invade the myometrium are referred to as adenomyosis.

The clinical presentation of endometriosis is variable; see Figure 20.7 for common symptoms.

Figure 20.7 Symptoms of endometriosis

[NB1]

- chronic pelvic pain [NB2]
- dysmenorrhoea (painful periods)
- dyspareunia (painful intercourse)
- dyschesia (difficult defecation)
- dysuria (painful urination)
- cyclical haematuria
- premenstrual spotting
- heavy menstrual bleeding
- period-related (catamenial) gastrointestinal symptoms (eg diarrhoea, occasionally painful abdominal bloating)
- infertility

NB1: Symptoms are not listed in order of frequency.

NB2: Chronic pain of endometriosis is defined as lasting 6 months or more. It can be constant or intermittent; acyclical pain can occur in individuals who also experience dysmenorrhoea.

A diagnosis of endometriosis should be considered in females who are of reproductive age and present with any of these symptoms. In this topic, female is used to mean anyone presumed female at birth.

Endometriosis can develop or progress after menopause, but this is uncommon. In about 30% of individuals with endometriosis, diagnosis only occurs during investigation of infertility. Earlier diagnosis is important to reduce the likelihood of infertility and other complications, such as progression of debilitating pain and a marked reduction in quality of life.

Atypical symptoms such as vague abdominal or urinary symptoms and acyclical pelvic pain make diagnosis challenging, particularly in adolescence. Acyclical pelvic pain can be constant or intermittent, dull, throbbing or sharp and can be exacerbated with physical activity.

Consider endometriosis in individuals with acyclical symptoms, particularly in adolescence.

Individuals with an affected first-degree relative have a three- to ten-fold increased risk of endometriosis. Other risk factors include early age at menarche, shorter menstrual cycle length, and greater height.

The differential diagnosis of endometriosis includes primary dysmenorrhoea, uterine fibroids, pelvic inflammatory disease, ovarian cysts, ectopic pregnancy, irritable bowel syndrome, appendicitis, diverticulitis, and interstitial cystitis.

Take a thorough history of the duration and severity of symptoms, family history of endometriosis, and reproductive goals to guide treatment options. Encourage the individual to keep a diary of symptoms to help establish if they are cyclical, and to assess impact on quality of life. Perform a thorough abdominal examination to look for masses or abdominal lower quadrant tenderness. Offer a pelvic examination to look for tenderness of the adnexa or uterus or posterior vaginal fornix, pelvic masses, vaginal nodules or fixed pelvic organs. See Examination of the vulva and vagina for advice on reducing distress related to examination.

Ultrasound, ideally performed at a specialist gynaecological service, can aid diagnosis of endometriosis by detecting endometrial deposits on the ovary, peritoneum or pelvic cavity. It may also detect ectopic pregnancy, ovarian torsion, fibroids and ovarian cysts. A transvaginal scan is most accurate, but a transabdominal scan is an alternative if transvaginal ultrasound is not available, or is declined. Normal findings on an ultrasound scan, do not, however, exclude a diagnosis of endometriosis. Deep infiltrating endometriosis (where deposits invade tissues) is particularly challenging to detect and requires specific expertise for diagnosis.
Normal findings on an ultrasound scan do not exclude a diagnosis of endometriosis.

Although diagnostic laparoscopy with histopathological confirmation after biopsy is the gold standard for confirming endometriosis, it is not required in all individuals; see Indications for referral in endometriosis. Start treatment once a presumed clinical diagnosis is made, based on symptoms and examination findings (with or without supportive ultrasound findings).

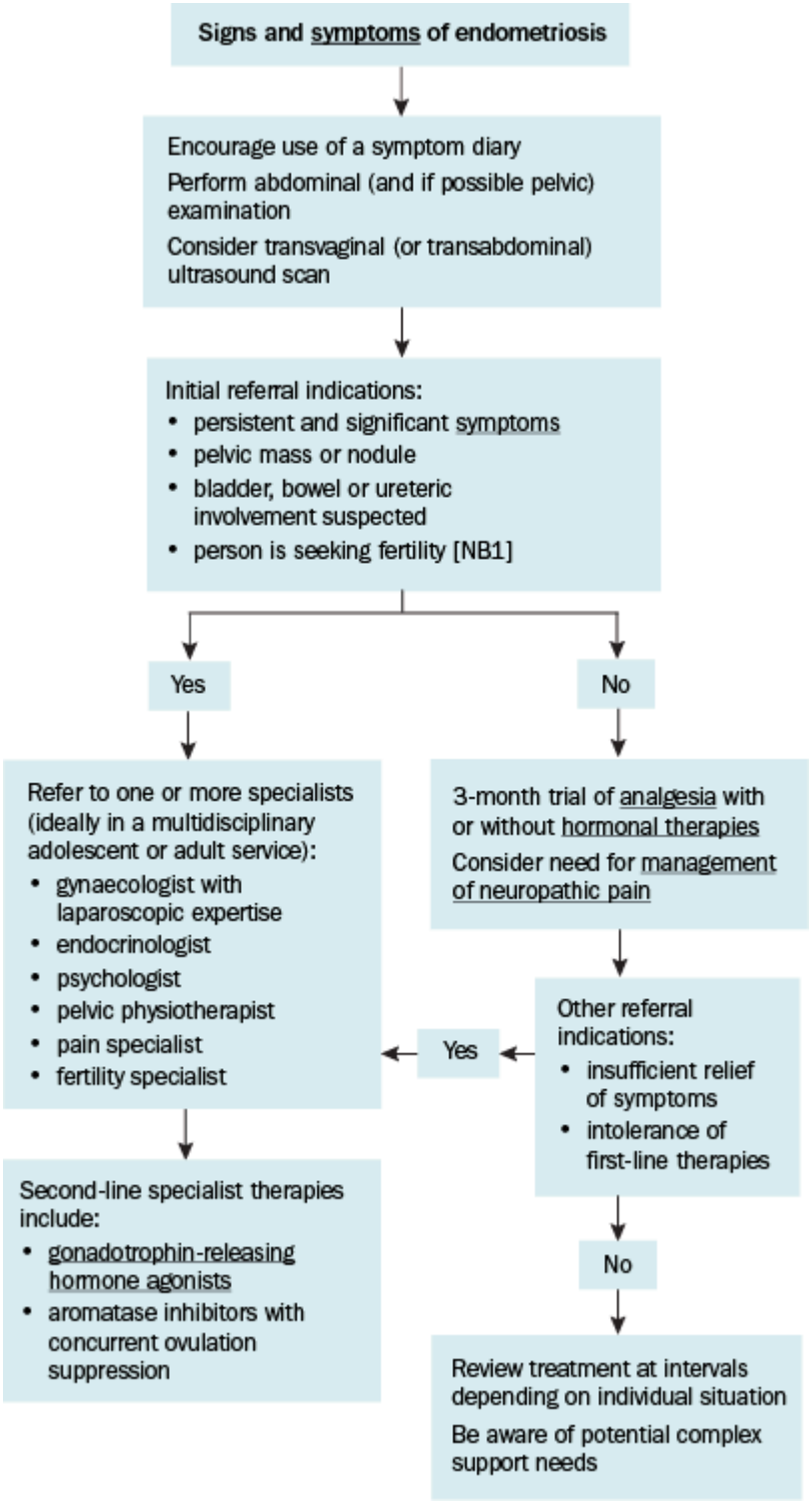
Start treatment for endometriosis once a presumed clinical diagnosis is made on history and examination.

Approach to treating endometriosis

Approach to treating endometriosis

The approach to treatment for endometriosis depends on the age of the patient, impact and severity of the symptoms and desire for fertility. See Figure 20.8.

Figure 20.8 Approach to managing endometriosis



NB1: Refer for fertility treatment for endometriosis if an individual is not able to conceive after 6 months of trying or is older than 35 years.

Analgesia and hormonal treatment are first-line therapies for endometriosis; they can be used alone or in combination.

Hormonal treatment for endometriosis includes combined hormonal contraception, and progestogens; specialist treatment includes gonadotrophin-releasing hormone (GnRH) agonists, or aromatase inhibitors combined with ovulation suppression. Treatment aims to reduce pain and suppress ovarian function (which induces atrophy of hormonally active endometriotic tissue).

Avoid hormonal treatment for individuals with endometriosis who are trying to conceive, because it can impair conception in the short term; see Endometriosis-related infertility. Hormonal treatment does not impair fertility in the long term.

Surgical management of endometriosis is indicated for treatment of severe pain or infertility. It involves laparoscopic removal or destruction of endometriotic tissue, or hysterectomy.

Patient information is available from the Royal Australian and New Zealand College of Obstetricians and Gynaecologists website and the Jean Hailes website.

Indications for referral in endometriosis

Indications for referral in endometriosis

Refer to a specialist endometriosis gynaecology service (if available) if the individual has:

- persistent and significant symptoms (see Figure 20.7)
- symptoms that do not respond to first-line treatment after 3 months
- a pelvic mass or nodule
- suspicion of bladder or bowel involvement with deep endometriosis.

Refer for fertility treatment for suspected or confirmed endometriosis if an individual is not able to conceive after 6 months of trying or is older than 35 years.

Other specialist input (ideally from a multidisciplinary team) may be required for individuals with complex needs, including from an endocrinologist, psychologist, pelvic physiotherapist or pain specialist.

Analgesia for endometriosis

Analgesia for endometriosis

Analgesics are first-line treatment of endometriosis-related pain; they may be used alone or together with hormonal therapies. A 3-month trial of a nonsteroidal anti-inflammatory drug (NSAID) or paracetamol (or a combination of both) is recommended; see Primary dysmenorrhoea for dosages. Pain may also have a neuropathic component because endometrial deposits have been shown to be innervated; correlations are seen between the degree of innervation and intensity of pain. See also Acute neuropathic pain and General principles of chronic pain management. Review response after 3 months to determine need for specialist referral.

Hormonal treatment for endometriosis

Hormonal treatment for endometriosis

Introduction to hormonal treatment for endometriosis

Introduction to hormonal treatment for endometriosis

Hormonal treatment can be started after a 3-month trial of analgesics, or at diagnosis, depending on the degree of bleeding and pain. Analgesia and hormone treatment can be used together.

Treatments include combined hormonal contraception (combined oral contraceptives [COCs] and the contraceptive vaginal ring) and progestogens (progestogen-only long-acting contraceptives or oral progestogens). No single option is known to be most effective; consider adverse effects and patient acceptability. Review response of hormone treatment after 3 months to assess adequacy of symptom relief and need for referral. Gonadotrophin-releasing hormone agonists and aromatase inhibitors may be prescribed by specialists.

Combined hormonal contraception for endometriosis

Combined hormonal contraception for endometriosis

Combined hormonal contraceptives can be used cyclically, but extended or continuous use is an option to eliminate menstruation, especially for management of dysmenorrhoea.

If an oral form of combined hormonal contraception is preferred for endometriosis, use:

combined oral contraceptive orally, once daily (see Table 20.12 for formulations). Advise extended or continuous use if wishing to avoid or minimise withdrawal bleeding or pain. *endometriosis*

If a nonoral form of combined hormonal contraception is preferred for endometriosis, use:

ethinylestradiol+etonogestrel 2.7+11.7 mg ring intravaginally. Leave ring in place for 3 consecutive weeks then remove. Insert new ring after 7 days. Advise extended or continuous use if wishing to avoid or minimise withdrawal bleeding or pain. *endometriosis*

Progestogens for endometriosis

Progestogens for endometriosis

Long-acting progestogens can be used first line for endometriosis as an alternative to combined hormonal contraception, particularly if estrogen is contraindicated. They offer effective symptom management and contraception and require less user involvement.

Long-acting progestogens suitable for endometriosis include the 52 mg levonorgestrel-releasing intrauterine contraceptive device (LNG-IUD), etonogestrel implant, and medroxyprogesterone depot injection.

For treatment of endometriosis with a long-acting progestogen, use:

1 etonogestrel 68 mg implant, subdermally. Replace every 3 years *endometriosis*

OR

1 levonorgestrel-releasing IUD 52 mg inserted into the uterus. Replace every 5 years *endometriosis*

OR

1 medroxyprogesterone 150 mg by deep intramuscular injection, every 12 weeks. *endometriosis*

Oral progestogens are indicated if there is a contraindication to estrogens and long-acting progestogens. Patient acceptability of oral progestogens is poor due to the adverse effects such as breast tenderness, irregular bleeding and headaches. The usual length of treatment is 3 to 6 months, but longer or repeat courses are common. Their long-term use is limited by the risk of hypoestrogenism (affecting bone and possibly cardiovascular health).

Oral progestogens used for endometriosis reduce the likelihood of conception, but adequate contraception is not assured. Use an effective nonhormonal method of contraception if contraception is desired.

If an oral progestogen is appropriate for endometriosis, common regimens are:

1 norethisterone 5 to 10 mg orally, once daily; increase to 10 mg twice daily if spotting occurs *endometriosis*

OR

2 dienogest 2 mg orally, once daily *endometriosis*

OR

2 medroxyprogesterone 10 mg orally, three times daily.

Danazol is reserved for use by specialists when other treatments are not tolerated. It has significant adverse effects (eg hirsutism, acne, voice change, liver toxicity, dyslipidaemia, a small increase in the risk of ovarian cancer), and treatment duration is limited to 6 to 9 months. An effective nonhormonal method of contraception must be used concurrently during treatment with danazol.

Gonadotrophin-releasing hormone agonists for endometriosis

Gonadotrophin-releasing hormone agonists for endometriosis

Gonadotrophin-releasing hormone (GnRH) agonists include the goserelin implant and the nafarelin intranasal spray. Use of GnRH agonists for endometriosis requires specialist advice. They may be used after surgery, especially if endometriotic lesions were not completely excised, or when other treatments have failed.

Contraception must be used concurrently during treatment with GnRH agonists.

GnRH agonists may cause hypoestrogenic adverse effects (eg hot flushes, vaginal dryness, decreased bone mineral density), which limit their duration of use to 6 months. Estrogen and progestogen replacement (with doses typically used for combined menopausal hormone therapy) reduce these adverse effects, allowing GnRH agonist use for up to 2 years. Use GnRH agonists with caution in young people, particularly adolescents, because GnRH agonists may limit peak bone mass.

Suitable regimens for GnRH agonists for endometriosis include:

1 goserelin 3.6 mg implant subcutaneously every 4 weeks (for up to 6 months) *endometriosis*

OR

1 nafarelin 200 micrograms intranasally, twice daily for 6 months (1 spray into one nostril in the morning and 1 spray into the other nostril in the evening). Increase to 400 micrograms twice daily (1 spray into each nostril morning and evening) according to response. *endometriosis*

Intranasal decongestants should not be used for at least 30 minutes after nafarelin as they may reduce its absorption.

Laparoscopy for endometriosis

Laparoscopy for endometriosis

Introduction to laparoscopy

Introduction to laparoscopy

Initial laparoscopy is sometimes required to make a definite diagnosis of endometriosis (see Indications for referral in endometriosis); in other cases, management is based on a presumed clinical diagnosis. Ideally, laparoscopy should be performed by a gynaecologist who is an expert in endometriosis surgery. Some deposits may be excised or ablated during an initial diagnostic laparoscopy. Subsequent treatment should favour medical management rather than laparoscopic surgery, to avoid scarring from repeated procedures, especially if the individual wants to conceive.

Further excisions or ablations are indicated to treat:

- infertility
- recurrent endometriosis (despite ongoing medical and/or previous surgical treatment)
- complications of endometriosis (eg bowel adhesions)
- deep endometriosis involving the bowel, bladder or ureter.

Laparoscopic hysterectomy for endometriosis

Laparoscopic hysterectomy for endometriosis

Hysterectomy is considered if there is evidence of adenomyosis on ultrasound (endometrial-like tissue in the myometrium) or if heavy menstrual bleeding has not responded to previous therapy.

Hysterectomy with bilateral salpingo-oophorectomy is beneficial in managing symptoms of endometriosis, but, if performed in premenopausal individuals, subsequent menopausal hormone therapy is required to protect other aspects of health (eg cardiovascular and bone health); see advice on premature ovarian insufficiency and early menopause for more information.

Ongoing management for endometriosis

Ongoing management for endometriosis

Ongoing management of endometriosis depends on treatment response, persisting symptoms, and expected health outcomes. Ongoing management includes:

- liaison with the treating gynaecologist regarding ongoing follow-up of deep endometriosis (including deep infiltrating endometriosis) or endometriomas in individuals who choose not to have surgery
- creating a management plan to help address symptoms and the physical and mental health aspects of endometriosis
- involving a pelvic floor physiotherapist for treatment of pelvic floor muscle dysfunction, persistent pelvic pain and dyspareunia
- referral to a counsellor or psychologist to assess mental and emotional health
- referral to a pain specialist.

There is no established evidence of benefit from complementary therapies in the management of dysmenorrhoea and pain related to endometriosis.

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Definition and causes of hirsutism

Definition and causes of hirsutism

Hirsutism is defined as excessive terminal hair in females (in this topic, female is used to mean anyone presumed female at birth) that is distributed in a male pattern. Terminal hair is coarse and pigmented, unlike vellus hair, which is fine, soft and relatively unpigmented. In hirsutism, androgens induce vellus follicles in sex-specific areas of the body to develop into terminal hairs. Hirsutism may affect only one region (eg lower face) or may be widespread (eg including limbs, chest, and midline of trunk).

Hirsutism should be differentiated from hypertrichosis, a widespread overgrowth of non–androgen-dependent hair in areas like the forehead and forearms. Occasionally, hypertrichosis is an adverse effect of drugs (eg ciclosporin, minoxidil, penicillamine, phenytoin).

Hirsutism results from:

- androgen excess of ovarian origin (biochemical hyperandrogenism caused by polycystic ovarian syndrome) in 70 to 80% of cases
- an increased responsiveness of the hair follicles to normal circulating androgens (idiopathic hirsutism) in 5 to 20% of cases.

Less common causes of hirsutism include:

- nonclassical congenital adrenal hyperplasia
- androgen-secreting tumours of the ovaries or adrenal glands
- Cushing syndrome
- exogenous corticosteroids or accidental transfer of topical testosterone from a partner
- sodium valproate therapy.

Diagnosing hirsutism

Diagnosing hirsutism

Approach to diagnosis of hirsutism

Approach to diagnosis of hirsutism

Diagnosis of hirsutism requires:

- clinical assessment
- investigation for underlying treatable conditions (regardless of the severity of the hirsutism). Underlying polycystic ovary syndrome (PCOS) is commonly identified. Rapid investigation is required if features suggestive of an androgen-secreting tumour are present, although these are less common.

If there is no evidence of endocrine abnormalities other than hirsutism, the condition may be idiopathic. Diagnosis of idiopathic hirsutism requires demonstration of normal serum testosterone concentration and free androgen index, and exclusion of PCOS (see Features and diagnosis of PCOS).

Clinical diagnosis of hirsutism

Clinical diagnosis of hirsutism

The Ferriman-Gallwey score can be used to diagnose and assess the severity of hirsutism; an online tool is available from the Endocrine Society. Thresholds used to define hirsutism vary among ethnic groups.

Ask about the distribution of excess hair to distinguish hirsutism from hypertrichosis. Establish the timeframe in which it has developed; rapid onset is suggestive of adrenal or ovarian tumours.

Ask about features of PCOS, particularly menstrual disturbance, and exclude exposure to exogenous steroids, topical testosterone or oral sodium valproate therapy. Also examine for signs of PCOS, such as obesity or acne.

Assess all females with hirsutism (or with a combination of localised excess hair and abnormal menstrual patterns), regardless of severity, for an underlying cause; the likelihood of elevated serum androgen concentrations cannot be predicted by severity of hirsutism.

Assess all females with hirsutism for an underlying cause.

Imaging and specialist referral are required if any **features suggestive of an androgen-secreting tumour** (ovarian or adrenal) are present, such as:

- rapid onset of hirsutism
- onset of hirsutism in a postmenopausal female
- virilising features such as clitoromegaly, voice deepening, development of muscular body habitus or breast atrophy.

Also consider whether hirsutism is a feature of:

- Cushing syndrome, which may cause central obesity, facial puffiness, peripheral oedema and skin thinning
- nonclassical congenital adrenal hyperplasia, which can be clinically indistinguishable from PCOS; it may be differentiated on laboratory investigations.

Laboratory investigations for hirsutism

Laboratory investigations for hirsutism

Laboratory investigation to detect biochemical hyperandrogenism (elevated total serum testosterone concentration or elevated free androgen index) is required in all females with hirsutism or other features of PCOS. Measure:

- **total serum testosterone concentration**—a result more than twice the upper limit of normal requires imaging to exclude androgen-secreting tumours of the ovaries or adrenal glands
- **free androgen index (FAI)**—this is calculated as total serum testosterone concentration divided by sex hormone–binding globulin (SHBG) concentration, multiplied by 100; it is preferred for diagnosis of biochemical hyperandrogenism because it is more sensitive than total serum testosterone concentration
- **serum 17-hydroxyprogesterone concentration** (measured during the follicular phase of the menstrual cycle)—elevation during the luteal phase of the menstrual cycle is physiologically normal, but elevation during the follicular phase may indicate nonclassical congenital adrenal hyperplasia
- **serum luteinising hormone (LH), estradiol and progesterone concentrations**—used to confirm that the individual is in the follicular phase of the menstrual cycle to avoid misinterpretation of serum 17-hydroxyprogesterone concentration
- **serum thyroid stimulating hormone (TSH) concentration**—hypothyroidism can cause elevated TSH, low SHBG and elevated FAI.

All of the above must be measured in the morning, preferably in the first week of a menstrual cycle, or on any convenient day if the individual is amenorrhoeic [Note 1].

Defer testing until at least 3 months have elapsed since any estrogen was taken. Estrogen-containing medications (eg combined hormonal contraception, menopausal hormone therapy) should not be used for at least 3 months before these tests because they elevate serum concentrations of SHBG, which lowers the FAI.

In females with features that may indicate Cushing syndrome (eg central obesity, facial puffiness, peripheral oedema, skin thinning), also consider other diagnostic tests (see Cushing syndrome).

Note 1: Do not delay testing or referral in females with very irregular menstrual cycles by waiting for a menstrual period.

Imaging for diagnosis of hirsutism

Imaging for diagnosis of hirsutism

If features suggestive of an androgen-secreting tumour are present, arrange adrenal magnetic resonance imaging (MRI) or computed tomography (CT) to assess for adrenal tumours, and an ovarian ultrasound scan (preferably transvaginal) to assess for ovarian tumours.

In females with hirsutism but no menstrual disturbance or biochemical hyperandrogenism, an ovarian ultrasound scan is indicated to assess or exclude PCOS.

A transvaginal ultrasound scan is preferred over a transabdominal scan for investigation of hirsutism, because it is gives better detail, including more reliable follicle counts used in diagnosis of PCOS. A transabdominal approach is an alternative if a transvaginal scan is not available or is declined.

Referral indications for diagnosis of hirsutism

Referral indications for diagnosis of hirsutism

Refer to a specialist if:

- a diagnosis other than idiopathic hirsutism or PCOS is suspected
- total serum testosterone concentration is more than twice the upper limit of normal
- serum 17-hydroxyprogesterone concentration is elevated during the follicular phase of the menstrual cycle (suggesting a diagnosis of congenital adrenal hyperplasia).

Approach to treating hirsutism

Approach to treating hirsutism

Determine the cause of hirsutism before starting treatment (other than physical treatments).

Hirsutism management is long-term. Treatment options in general practice are:

- physical measures to remove unwanted hair
- combined oral contraception (COC)
- menopausal hormone therapy (MHT)
- antiandrogen therapy.

Physical measures achieve effects rapidly; they can be used alone or started concurrently with other therapies. COC therapy (or MHT therapy in postmenopausal individuals) is the mainstay of treatment for hirsutism; however, treatment is usually required for at least 6 months before an effect is seen. Compounded eflornithine cream can be considered if a more immediate effect is required (as it has an effect within 6 to 8 weeks), but is expensive and generally reserved for treatment of facial hair.

Antiandrogen therapy can be added if response to COC or MHT therapy is insufficient after 6 months, or can be used alone if COC or MHT therapy is contraindicated.

Refer to a specialist if response to antiandrogen therapy is insufficient after 6 to 12 months of treatment.

Glucocorticoid therapy may be used by specialists to treat hirsutism in females with nonclassical congenital adrenal hyperplasia.

Physical measures to treat hirsutism

Physical measures to treat hirsutism

Physical measures have a major role in managing hirsutism. They include simple measures such as waxing, plucking, shaving and depilatory creams, and more intensive methods such as epilation by intense pulsed light therapy (IPL), laser therapy or electrolysis. Their effect is more immediate than drug therapy.

Physical measures are suitable:

- when drug therapy is contraindicated (eg when planning a pregnancy)
- for individuals reluctant to use drug therapy
- as an adjunct to drug therapy.

Contrary to common belief, shaving does not accelerate hair growth.

Epilation by IPL, laser or electrolysis can be time consuming and expensive. IPL and laser epilation are most suitable for individuals with fair skin and dark hair; results can last 6 to 9 months. Antiandrogen therapy during and after laser epilation helps prevent regrowth. Electrolysis, performed by a skilled operator, may have a more permanent benefit than IPL or laser treatment; it destroys hair follicles, but some regrowth occurs.

Bleaching may make hirsutism less obvious in individuals with fair skin.

Combined oral contraceptives for hirsutism

Combined oral contraceptives for hirsutism

Combined oral contraceptives (COCs) are the preferred hirsutism treatment in premenopausal individuals, and in those with menstrual irregularity or amenorrhoea, since cycle control is a major benefit of COCs.

Combined oral contraceptives (COCs) treat hirsutism by suppressing gonadotrophin-driven androgen production. They also reduce bioavailable testosterone by increasing serum sex hormone–binding globulin (SHBG) concentration.

No specific types or doses of estrogen, progestogen or combinations are preferred for the treatment of hirsutism. Although COCs containing antiandrogenic progestogens (eg cyproterone, dienogest, drospirenone) may have added benefit compared to formulations with other progestogens, there are limited head-to-head comparisons and insufficient data to recommend specific formulations.

For treatment of hirsutism with a COC, use:

combined oral contraceptive orally, once daily (see Table 20.12 for formulations). Advise a tailored regimen if wishing to avoid or minimise withdrawal bleeding. *hirsutism*

If a nonoral method is preferred, the contraceptive vaginal ring can be used.

Progestogen-only contraceptives are not effective and may worsen hirsutism.

Avoid progestogen-only contraceptives in females with hirsutism.

If hirsutism does not respond to COC after 6 months, consider repeating laboratory investigations. If biochemical hyperandrogenism has not responded, consider investigating for nonclassical congenital adrenal

hyperplasia. Also consider imaging to exclude another cause such as an adrenal or ovarian tumour. If biochemical hyperandrogenism has been suppressed but clinical response is inadequate, consider adding an antiandrogen.

Menopausal hormone therapy for hirsutism

Menopausal hormone therapy for hirsutism

Menopausal hormone therapy (MHT) is used in postmenopausal individuals with hirsutism. See Systemic MHT in individuals with hirsutism for advice on formulations most likely to be effective.

If hirsutism does not respond to MHT after 6 months, consider repeating laboratory investigations. If biochemical hyperandrogenism has not responded, consider investigating for nonclassical congenital adrenal hyperplasia. Also consider imaging to exclude another cause such as an adrenal or ovarian tumour. If biochemical hyperandrogenism has been suppressed but clinical response is inadequate, consider adding an antiandrogen.

Antiandrogen therapy for hirsutism

Antiandrogen therapy for hirsutism

Overview of antiandrogen therapy for hirsutism

Overview of antiandrogen therapy for hirsutism

Antiandrogens used in hirsutism include spironolactone, cyproterone, and the 5-alpha-reductase inhibitors finasteride and dutasteride. Choice of antiandrogen is influenced by adverse effect profile and pharmacokinetics; see Table 20.25. Dutasteride should be reserved for specialist use because data on its efficacy are limited and it has a very long half-life, which increases its risk of teratogenicity.

Adding an antiandrogen to a combined oral contraceptive (COC) or menopausal hormone therapy (MHT) is beneficial in females who do not respond adequately to 6 months of treatment with either therapy alone.

An antiandrogen can be used alone if a COC or MHT is contraindicated, but if used alone in females of reproductive age, a highly effective method of contraception must be used concurrently.

Antiandrogens are contraindicated in pregnancy.

Antiandrogen use in pregnancy may increase the risk of defective virilisation of the male fetus. Antiandrogens should be stopped when planning pregnancy or if unplanned pregnancy occurs. The risk of unintended drug exposure during pregnancy and therefore potential teratogenicity depends on the half-life:

- finasteride and spironolactone have short half-lives (less than 24 hours); they should be stopped when the individual starts trying to conceive
- cyproterone has a longer half-life (up to 57 hours); it should be stopped 2 to 3 months before trying to conceive. Timing is influenced by individual factors (eg kidney function); seek specialist advice if there is any uncertainty [Note 2].

Table 20.25 Comparison of antiandrogens used for hirsutism

Drugs
spironolactone
cyproterone
finasteride

Spironolactone

Use in females of reproductive age	use with highly effective contraception (preferably COC to avoid irregular bleeding)
	stop when trying to conceive
Use in postmenopausal females	can be used but assess kidney function before treatment and after 3 months
	risk of hyperkalaemia and acidosis in some patient groups
Significant adverse effects [NB1]	can cause occasional hypotension and polyuria
	use alone may cause amenorrhoea or irregular bleeding (mainly in pre- and perimenopausal individuals)
Cyproterone	
Use in females of reproductive age	use with highly effective contraception (preferably COC to avoid hypoestrogenism)
	stop 2 to 3 months before trying to conceive; seek specialist advice if any uncertainty (eg altered kidney function)
Use in postmenopausal females	generally not advised as low-dose formulations are not available
Significant adverse effects [NB1]	amenorrhoea common
	weight gain
	fatigue
	breast tenderness
	reduced libido
Finasteride	
Use in females of reproductive age	use with highly effective contraception
	stop when trying to conceive
Use in postmenopausal females	can be used but cost may be a concern
	can be used but cost may be a concern
Significant adverse effects [NB1]	uncommon, but limited data

COC= combined oral contraceptive

NB1: For further information on adverse effects, see Australian product information.

Note 2: This timeframe for stopping cyproterone before conception does not apply to oral contraceptives containing low-dose cyproterone.

Spironolactone for hirsutism

Spironolactone for hirsutism

Spironolactone acts in various ways in hirsutism; it is a mineralocorticoid antagonist, an androgen receptor antagonist at the hair follicle, and a weak 5-alpha-reductase inhibitor. It also has a weak progestogenic effect and, if used alone, can lead to irregular uterine bleeding or amenorrhoea; ideally, it should be used in combination with a COC to avoid this.

A typical regimen is:

spironolactone 100 mg orally, once daily. If no benefit is apparent after 6 months, increase to 200 mg daily. *hirsutism*

Spironolactone can cause hyperkalaemia, particularly in patients with kidney impairment, and those taking angiotensin converting enzyme inhibitors (ACEI) or angiotensin II receptor blockers (ARB). Consider assessing kidney function and serum potassium concentration before starting therapy and monitor periodically. Advise patients to avoid potassium supplements while taking spironolactone.

Spironolactone is well tolerated, but polyuria and postural hypotension may occur at the start of treatment; consider reducing dose to 50 mg if these effects occur.

Cyproterone for hirsutism

Cyproterone for hirsutism

Cyproterone is used in hirsutism for its antiandrogen action. It also has a pronounced progestogenic effect and suppresses ovarian androgen production. However, cyproterone also interacts with glucocorticoid receptors, which may explain weight gain seen with high doses.

If used alone, cyproterone usually leads to oligomenorrhoea or amenorrhoea and hypoestrogenism. Therefore, it should be used together with a COC in premenopausal or perimenopausal individuals. Use of cyproterone is generally not recommended in postmenopausal individuals because low-dose formulations are not available; doses available to treat hirsutism may be associated with increased risk of breast cancer and cardiovascular disease in postmenopausal individuals.

Cyproterone is usually given for the first 10 days of each COC cycle. This permits the effect of cyproterone to wear off before the hormone-free interval of the COC cycle if an individual wishes to have a withdrawal bleed. The withdrawal bleed may be delayed because of the long half-life of cyproterone. If it is delayed for more than 1 week, a pregnancy test should be considered.

For females who are premenopausal or perimenopausal, use:

cyproterone 50 mg orally, once daily for 10 days per month, starting on the first day of the cycle of a combined oral contraceptive (see Table 20.12 for formulations). If response is inadequate after 3 months, increase to 100 mg daily. Once maximal effect is achieved, consider reducing or stopping cyproterone. *hirsutism*

Adverse effects of cyproterone include fatigue, weight gain, breast tenderness and reduced libido.

Prolonged use of 40 mg to 200 mg daily of cyproterone has been associated with the development of meningiomata. A causal link has not been proven, but tumour shrinkage has been reported in some cases after stopping the drug. Current guidelines do not advocate routine monitoring for meningiomata. However, once maximal effect is achieved, consider reducing or stopping cyproterone because of the possibility of increased meningioma risk.

5-alpha-reductase inhibitors for hirsutism

5-alpha-reductase inhibitors for hirsutism

The 5-alpha-reductase inhibitors finasteride and dutasteride block the conversion of testosterone to dihydrotestosterone, the active androgen in skin. Neither drug is approved by the Australian Therapeutic Goods Administration (TGA) for the treatment of hirsutism.

Finasteride has similar effect to other antiandrogens, but it is more costly. It must be combined with a highly effective method of contraception, unless there is no risk of conception (eg the individual has had a hysterectomy or tubal ligation, is postmenopausal, or only has same-sex partners). Limited data on adverse effects of finasteride from small studies suggest they are not common. A typical regimen is:

finasteride 2.5 to 5 mg orally, once daily. *hirsutism*

Dutasteride should be reserved for specialist use because its efficacy has not been proven in a randomised controlled trial. It is usually only used in postmenopause; it has an extremely long half-life (4 to 5 weeks), so teratogenic risk persists for months after it is stopped.

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Features and diagnosis of polycystic ovary syndrome

Features and diagnosis of polycystic ovary syndrome

Polycystic ovary syndrome (PCOS) is a reproductive and metabolic disorder affecting females of reproductive age (in this topic, female is used to mean anyone presumed female at birth). PCOS affects 8 to 13% of females of reproductive age; the prevalence appears to be higher in Aboriginal and Torres Strait Islander peoples.

Consider the possibility of PCOS in females presenting with menstrual disturbance, hirsutism or premenopausal alopecia. Acne is less strongly associated with PCOS, but PCOS should be considered if hirsutism, alopecia, menstrual disturbance or obesity are also present. Before confirming a diagnosis of PCOS, exclude other causes of presenting features.

Diagnosis of PCOS requires exclusion of differential diagnoses.

A diagnosis is made if an adult meets **two of the following diagnostic criteria** and other causes have been excluded:

- menstrual disturbance, including secondary oligomenorrhoea or amenorrhoea
- clinical or biochemical hyperandrogenism
- polycystic appearance of ovaries on ultrasound.

Additional features of PCOS (which are not essential for diagnosis) include:

- obesity
- insulin resistance (with a tendency to develop type 2 diabetes)
- subfertility

An ultrasound scan is not required for the diagnosis of PCOS if an adult has both menstrual disturbance and clinical or biochemical hyperandrogenism. If only one of these features is present, a transvaginal ultrasound should be performed in the first half of the menstrual cycle, and a follicle count should be requested [Note 1].

PCOS can be diagnosed without ultrasound if an adult has both menstrual disturbance and clinical or biochemical hyperandrogenism.

Refer adolescents with suspected PCOS for specialist assessment because interpretation of clinical features and ultrasound findings in adolescence is complex. Menstrual irregularity is only considered abnormal if it persists for more than 2 years post menarche. Normal adolescent ovaries may have a polycystic appearance for up to 8 years, so ultrasound is not recommended.

Refer adolescents with suspected PCOS for specialist assessment.

Note 1: A transvaginal ultrasound scan is preferred because it is gives best detail, including more reliable follicle counts used in diagnosis of PCOS. A transabdominal approach is an alternative when a transvaginal scan is not available, or is declined.

Approach to treating polycystic ovary syndrome

Approach to treating polycystic ovary syndrome

Treatment of polycystic ovary syndrome (PCOS) aims to address the symptoms and long-term health risks arising from abnormal follicular development and ovarian hormone synthesis, while taking account of the individual's goals for treatment. Symptoms and health risks of PCOS include:

- consequences of anovulatory menstrual cycles
  - irregular menstrual bleeding of variable volume
  - a lack of progesterone-induced endometrial shedding, which leads to proliferation of the endometrium and increased risk of endometrial cancer
  - subfertility
- consequences of excess ovarian androgen production
  - hirsutism
  - acne
  - androgenetic alopecia
- obesity, which affects the majority of individuals with PCOS and increases the risk of complications
- insulin resistance
  - exacerbation of hyperandrogenism
  - increased risk of type 2 diabetes and cardiovascular disease
- additional cardiovascular risk factors such as dyslipidaemia
- poor mental health (in particular, body-image concerns related to excess weight and hirsutism).

Most aspects of PCOS can be managed in general practice, but specialist referral is appropriate if:

- diagnosis is uncertain (eg in adolescents)
- hirsutism is not responding to antiandrogen therapy after 6 to 12 months
- seeking fertility treatment.

For more detailed information on the management of PCOS, see the International evidence-based guideline for the assessment and management of polycystic ovary syndrome and the PCOS Practice Tools for Health Practitioners.

Metformin for individuals with polycystic ovary syndrome

Metformin for individuals with polycystic ovary syndrome

Metformin improves glucose metabolism by decreasing glucose production in the liver and increasing glucose uptake in tissues. Although specific evidence of its impact on insulin resistance in polycystic ovary syndrome (PCOS) is limited, it can be considered for individuals with PCOS who have:

- a high risk of developing type 2 diabetes, even if tests of glucose metabolism are normal
- subfertility in an individual with irregular menstrual cycles (despite lifestyle change)
- a body mass index (BMI) greater than 25 kg/m^2 if insufficient weight is lost after a 6-month trial of lifestyle changes (metformin does not cause significant weight loss but may prevent weight gain); see also Weight control in PCOS.

Metformin also **suppresses ovarian androgen production**, which improves the frequency of ovulation in individuals with PCOS. Although it is not recommended for managing irregular bleeding, it can be used in managing subfertility.

If metformin is indicated, use:

1 metformin immediate-release 500 mg orally, daily with evening meal as an initial dose; increase daily dose by 500 mg every 1 to 2 weeks as tolerated, up to a maximum of 1500 mg daily in 2 or 3 divided doses
polycystic ovary syndrome

OR

2 metformin modified-release 500 mg orally, daily with evening meal as an initial dose; increase daily dose by 500 mg every 1 to 2 weeks as tolerated, up to a maximum of 1500 mg daily.

Most studies of metformin for PCOS used immediate-release metformin. Gastrointestinal effects of immediate-release metformin can be minimised by starting treatment at a low dose, titrating gradually, and taking with food. If this is not tolerated, modified-release metformin may be used.

If type 2 diabetes is diagnosed in an individual with PCOS, see Metformin for adults with type 2 diabetes for information on metformin dosage, mode of action and adverse effects.

Menstrual disturbance and polycystic ovary syndrome

Menstrual disturbance and polycystic ovary syndrome

Overview of menstrual disturbance and polycystic ovary syndrome

Overview of menstrual disturbance and polycystic ovary syndrome

Many individuals with polycystic ovary syndrome (PCOS) have anovulatory cycles resulting in menstrual disturbance, including:

- irregular menstrual cycles of unusual length or variability
- oligomenorrhoea or amenorrhoea

Prolonged estrogenic stimulation of the endometrium during anovulatory cycles, without progestogen-induced shedding, causes endometrial thickening. This can result in heavy bleeding when menstruation does occur, and increases the risk of endometrial cancer 2-to 6-fold. Fertility is reduced in individuals with PCOS who have menstrual disturbance, but conception can occur even if menstruation occurs only occasionally; see PCOS and subfertility.

In those not wishing to conceive, menstrual regulation aims to control bleeding and provide protection from estrogen-induced endometrial cancer. Investigate heavy menstrual bleeding that persists despite 6 months of therapy to exclude endometrial cancer. Investigate earlier if there are additional features that increase cancer risk.

Treatment of menstrual disturbance in individuals with polycystic ovary syndrome

Treatment of menstrual disturbance in individuals with polycystic ovary syndrome

Combined oral contraceptives (COCs) provide the most effective menstrual regulation in PCOS; they also provide effective contraception. They have the added benefit of suppressing ovarian androgen production, which can be beneficial for hirsutism, acne and androgenetic alopecia. Although some small studies of COCs have shown an adverse effect on glucose metabolism, a meta-analysis did not find that they worsen insulin resistance in individuals with PCOS [Note 2].

Combined oral contraceptives provide the most effective menstrual regulation in PCOS.

Although COCs containing antiandrogenic progestogens (eg cyproterone dienogest, drospirenone) may have added benefit compared to formulations with other progestogens, there are limited head-to-head comparisons and insufficient data to recommend specific formulations.

Use the lowest dose of estrogen that effectively controls the menstrual cycle. Use:

combined oral contraceptive orally, once daily (see Table 20.12 for formulations). Advise extended or continuous use to avoid or minimise withdrawal bleeding. *polycystic ovary syndrome*

If COCs are contraindicated, the 52 mg levonorgestrel-releasing intrauterine contraceptive device (LNG-IUD) can be used to provide endometrial protection and contraception. Use:

levonorgestrel-releasing IUD 52 mg inserted into the uterus. Replace every 5 years. *polycystic ovary syndrome*

An **oral cyclical progestogen** can be considered for individuals who have a contraindication or preference to avoid COCs or the LNG-IUD. Oral cyclical progestogens induce endometrial shedding and provide endometrial protection; however, they should not be used long term because they:

- are less effective than the LNG-IUD for regulating menstruation
- do not address other aspects of PCOS such as hyperandrogenism
- are poorly tolerated (adverse effects include breast tenderness and headaches)
- confer a risk of hypoestrogenism (which affects bone health and possibly cardiovascular health).

If an oral cyclical progestogen is indicated, see Heavy menstrual bleeding for dosages.
Oral cyclical progestogens provide only short-term treatment for menstrual disturbance in PCOS.

Metformin may increase menstrual frequency in individuals with PCOS by inducing ovulation. However, metformin is not recommended for management of menstrual disturbance in individuals with PCOS (except to treat impaired fertility); it provides poor control of heavy bleeding and inadequate protection against endometrial hyperplasia and cancer.

Metformin is not recommended for management of menstrual disturbance in PCOS other than as part of treatment for subfertility.

Note 2: Halperin IJ, Kumar SS, Stroup DF, Laredo SE. The association between the combined oral contraceptive pill and insulin resistance, dysglycemia and dyslipidemia in women with polycystic ovary syndrome: a systematic review and meta-analysis of observational studies. Hum Reprod 2011;26(1):191-201. [URL]

Weight control in polycystic ovary syndrome

Weight control in polycystic ovary syndrome

Many individuals with polycystic ovary syndrome (PCOS) are overweight (have a body mass index [BMI] between 25 to 29 kg/m^2), obese (BMI of 30 kg/m^2 or more) or centrally obese. Obesity in individuals with PCOS increases the risk and severity of:

- menstrual disturbance
- infertility
- obstructive sleep apnoea
- insulin resistance and type 2 diabetes
- cardiovascular disease
- poor mental health
- nonalcoholic fatty liver disease.

In overweight individuals with PCOS, losing 5% of total body weight results in:

- reduced insulin resistance and hyperandrogenism
- improved ovulatory function, fertility and psychological wellbeing.

Losing 5% of total body weight improves metabolic, reproductive and mental health in individuals with PCOS.

For information on weight management, see General principles of management of excess body weight.

If lifestyle measures are not effective in managing weight after 6 months, consider adding metformin. Metformin does not cause significant weight loss but may prevent weight gain.

Consider metformin as an adjunct to lifestyle measures in weight management for individuals with PCOS.

Insulin resistance, impaired glucose tolerance and type 2 diabetes in polycystic ovary syndrome

Insulin resistance, impaired glucose tolerance and type 2 diabetes in polycystic ovary syndrome

Polycystic ovary syndrome (PCOS) is often associated with insulin resistance. Consequences of insulin resistance include:

- exacerbation of ovarian androgen overproduction and suppression of sex hormone–binding globulin (SHBG), leading to increased bioavailability of androgens
- development of impaired glucose tolerance or type 2 diabetes; risk is increased several-fold compared to individuals without PCOS.

Individuals with PCOS at **high risk of type 2 diabetes** include those with:

- a body mass index (BMI) higher than 25 kg/m^2 for Caucasians or 23 kg/m^2 for Asians
- an impaired fasting serum glucose concentration
- impaired glucose tolerance
- a family history of diabetes
- a history of gestational diabetes
- hypertension
- high-risk ethnicity (eg Africans, Aboriginal and Torres Strait Islander peoples, and South East Asians).

Screen all individuals with PCOS using fasting blood glucose, HbA1c or an oral glucose tolerance test (OGTT), and repeat every 1 to 3 years. Initial screening with an OGTT is preferred in individuals with PCOS who are at high risk of type 2 diabetes, or who are contemplating pregnancy, because it is the most sensitive test.

Screen all individuals with PCOS for abnormalities of glucose metabolism every 1 to 3 years.

Dietary and exercise measures, as outlined for weight management, can improve insulin sensitivity and reduce the risk of developing type 2 diabetes. Although studies in individuals with PCOS are lacking, studies in other populations suggest exercise may reduce insulin resistance in the absence of weight loss.

Metformin is recommended for individuals at high risk of developing type 2 diabetes, even if current tests of glucose metabolism are normal. Metformin has also been shown to counter other sequelae of insulin resistance in PCOS (ovarian androgen overproduction and suppression of SHBG). For information on the role of metformin in PCOS, see here.

If an individual with PCOS is diagnosed with type 2 diabetes, see Metformin for adults with type 2 diabetes.

For further details on screening and management of insulin resistance, see the International evidence-based guideline for the assessment and management of polycystic ovary syndrome and the PCOS Practice Tools for Health Practitioners.

Cardiovascular risk in polycystic ovary syndrome

Cardiovascular risk in polycystic ovary syndrome

Individuals with polycystic ovary syndrome (PCOS) usually have risk factors for cardiovascular disease, such as excess weight, abnormal glucose metabolism or dyslipidaemia (low high-density lipoprotein cholesterol [HDL-C], high triglycerides); however, an increase in cardiovascular mortality in individuals with PCOS has not been conclusively proven.

Assess cardiovascular risk factors in all individuals with PCOS.

Assess absolute cardiovascular risk in all individuals with PCOS, and treat accordingly. See also the International evidence-based guideline for the assessment and management of polycystic ovary syndrome and the PCOS Practice Tools for Health Practitioners .

Mental health in polycystic ovary syndrome

Mental health in polycystic ovary syndrome

Polycystic ovary syndrome (PCOS) has symptoms and long-term implications for health that may lead to decreased quality of life and psychological morbidity. Assess psychological wellbeing in all individuals with PCOS and consider referral to a mental health professional.

Assess psychological wellbeing in all individuals with PCOS.

Weight gain and hirsutism are the most frequently reported concerns associated with psychological morbidity; the risks of poor body image, eating disorders and sexual difficulties are increased. For further information, see the International evidence-based guideline for the assessment and management of polycystic ovary syndrome and the PCOS Practice Tools for Health Practitioners .

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Features and diagnosis of polycystic ovary syndrome

Polycystic ovary syndrome (PCOS) is a reproductive and metabolic disorder affecting females of reproductive age (in this topic, female is used to mean anyone presumed female at birth). PCOS affects 8 to 13% of females of reproductive age; the prevalence appears to be higher in Aboriginal and Torres Strait Islander peoples.

Consider the possibility of PCOS in females presenting with menstrual disturbance, hirsutism or premenopausal alopecia. Acne is less strongly associated with PCOS, but PCOS should be considered if hirsutism, alopecia, menstrual disturbance or obesity are also present. Before confirming a diagnosis of PCOS, exclude other causes of presenting features.

Diagnosis of PCOS requires exclusion of differential diagnoses.

A diagnosis is made if an adult meets **two of the following diagnostic criteria** and other causes have been excluded:

- menstrual disturbance, including secondary oligomenorrhoea or amenorrhoea
- clinical or biochemical hyperandrogenism
- polycystic appearance of ovaries on ultrasound.

Additional features of PCOS (which are not essential for diagnosis) include:

- obesity
- insulin resistance (with a tendency to develop type 2 diabetes)
- subfertility

An ultrasound scan is not required for the diagnosis of PCOS if an adult has both menstrual disturbance and clinical or biochemical hyperandrogenism. If only one of these features is present, a transvaginal ultrasound should be performed in the first half of the menstrual cycle, and a follicle count should be requested [Note 1].

PCOS can be diagnosed without ultrasound if an adult has both menstrual disturbance and clinical or biochemical hyperandrogenism.

Refer adolescents with suspected PCOS for specialist assessment because interpretation of clinical features and ultrasound findings in adolescence is complex. Menstrual irregularity is only considered abnormal if it persists for more than 2 years post menarche. Normal adolescent ovaries may have a polycystic appearance for up to 8 years, so ultrasound is not recommended.

Refer adolescents with suspected PCOS for specialist assessment.

Note 1: A transvaginal ultrasound scan is preferred because it is gives best detail, including more reliable follicle counts used in diagnosis of PCOS. A transabdominal approach is an alternative when a transvaginal scan is not available, or is declined.

Approach to treating polycystic ovary syndrome

Approach to treating polycystic ovary syndrome

Treatment of polycystic ovary syndrome (PCOS) aims to address the symptoms and long-term health risks arising from abnormal follicular development and ovarian hormone synthesis, while taking account of the individual's goals for treatment. Symptoms and health risks of PCOS include:

- consequences of anovulatory menstrual cycles
  - irregular menstrual bleeding of variable volume
  - a lack of progesterone-induced endometrial shedding, which leads to proliferation of the endometrium and increased risk of endometrial cancer
  - subfertility
- consequences of excess ovarian androgen production
  - hirsutism
  - acne
  - androgenetic alopecia
- obesity, which affects the majority of individuals with PCOS and increases the risk of complications
- insulin resistance
  - exacerbation of hyperandrogenism
  - increased risk of type 2 diabetes and cardiovascular disease
- additional cardiovascular risk factors such as dyslipidaemia
- poor mental health (in particular, body-image concerns related to excess weight and hirsutism).

Most aspects of PCOS can be managed in general practice, but specialist referral is appropriate if:

- diagnosis is uncertain (eg in adolescents)
- hirsutism is not responding to antiandrogen therapy after 6 to 12 months
- seeking fertility treatment.

For more detailed information on the management of PCOS, see the International evidence-based guideline for the assessment and management of polycystic ovary syndrome and the PCOS Practice Tools for Health Practitioners.

Metformin for individuals with polycystic ovary syndrome

Metformin for individuals with polycystic ovary syndrome

Metformin improves glucose metabolism by decreasing glucose production in the liver and increasing glucose uptake in tissues. Although specific evidence of its impact on insulin resistance in polycystic ovary syndrome (PCOS) is limited, it can be considered for individuals with PCOS who have:

- a high risk of developing type 2 diabetes, even if tests of glucose metabolism are normal
- subfertility in an individual with irregular menstrual cycles (despite lifestyle change)
- a body mass index (BMI) greater than 25 kg/m^2 if insufficient weight is lost after a 6-month trial of lifestyle changes (metformin does not cause significant weight loss but may prevent weight gain); see also Weight control in PCOS.

Metformin also **suppresses ovarian androgen production**, which improves the frequency of ovulation in individuals with PCOS. Although it is not recommended for managing irregular bleeding, it can be used in managing subfertility.

If metformin is indicated, use:

1 metformin immediate-release 500 mg orally, daily with evening meal as an initial dose; increase daily dose by 500 mg every 1 to 2 weeks as tolerated, up to a maximum of 1500 mg daily in 2 or 3 divided doses
polycystic ovary syndrome

OR

2 metformin modified-release 500 mg orally, daily with evening meal as an initial dose; increase daily dose by 500 mg every 1 to 2 weeks as tolerated, up to a maximum of 1500 mg daily.

Most studies of metformin for PCOS used immediate-release metformin. Gastrointestinal effects of immediate-release metformin can be minimised by starting treatment at a low dose, titrating gradually, and taking with food. If this is not tolerated, modified-release metformin may be used.

If type 2 diabetes is diagnosed in an individual with PCOS, see Metformin for adults with type 2 diabetes for information on metformin dosage, mode of action and adverse effects.

Menstrual disturbance and polycystic ovary syndrome

Menstrual disturbance and polycystic ovary syndrome

Overview of menstrual disturbance and polycystic ovary syndrome

Overview of menstrual disturbance and polycystic ovary syndrome

Many individuals with polycystic ovary syndrome (PCOS) have anovulatory cycles resulting in menstrual disturbance, including:

- irregular menstrual cycles of unusual length or variability
- oligomenorrhoea or amenorrhoea

Prolonged estrogenic stimulation of the endometrium during anovulatory cycles, without progestogen-induced shedding, causes endometrial thickening. This can result in heavy bleeding when menstruation does occur, and increases the risk of endometrial cancer 2-to 6-fold. Fertility is reduced in individuals with PCOS who have menstrual disturbance, but conception can occur even if menstruation occurs only occasionally; see PCOS and subfertility.

In those not wishing to conceive, menstrual regulation aims to control bleeding and provide protection from estrogen-induced endometrial cancer. Investigate heavy menstrual bleeding that persists despite 6 months of therapy to exclude endometrial cancer. Investigate earlier if there are additional features that increase cancer risk.

Treatment of menstrual disturbance in individuals with polycystic ovary syndrome

Treatment of menstrual disturbance in individuals with polycystic ovary syndrome

Combined oral contraceptives (COCs) provide the most effective menstrual regulation in PCOS; they also provide effective contraception. They have the added benefit of suppressing ovarian androgen production, which can be beneficial for hirsutism, acne and androgenetic alopecia. Although some small studies of COCs have shown an adverse effect on glucose metabolism, a meta-analysis did not find that they worsen insulin resistance in individuals with PCOS [Note 2].

Combined oral contraceptives provide the most effective menstrual regulation in PCOS.

Although COCs containing antiandrogenic progestogens (eg cyproterone dienogest, drospirenone) may have added benefit compared to formulations with other progestogens, there are limited head-to-head comparisons and insufficient data to recommend specific formulations.

Use the lowest dose of estrogen that effectively controls the menstrual cycle. Use:

combined oral contraceptive orally, once daily (see Table 20.12 for formulations). Advise extended or continuous use to avoid or minimise withdrawal bleeding. *polycystic ovary syndrome*

If COCs are contraindicated, the 52 mg levonorgestrel-releasing intrauterine contraceptive device (LNG-IUD) can be used to provide endometrial protection and contraception. Use:

levonorgestrel-releasing IUD 52 mg inserted into the uterus. Replace every 5 years. *polycystic ovary syndrome*

An **oral cyclical progestogen** can be considered for individuals who have a contraindication or preference to avoid COCs or the LNG-IUD. Oral cyclical progestogens induce endometrial shedding and provide endometrial protection; however, they should not be used long term because they:

- are less effective than the LNG-IUD for regulating menstruation
- do not address other aspects of PCOS such as hyperandrogenism
- are poorly tolerated (adverse effects include breast tenderness and headaches)
- confer a risk of hypoestrogenism (which affects bone health and possibly cardiovascular health).

If an oral cyclical progestogen is indicated, see Heavy menstrual bleeding for dosages.
Oral cyclical progestogens provide only short-term treatment for menstrual disturbance in PCOS.

Metformin may increase menstrual frequency in individuals with PCOS by inducing ovulation. However, metformin is not recommended for management of menstrual disturbance in individuals with PCOS (except to treat impaired fertility); it provides poor control of heavy bleeding and inadequate protection against endometrial hyperplasia and cancer.

Metformin is not recommended for management of menstrual disturbance in PCOS other than as part of treatment for subfertility.

Note 2: Halperin IJ, Kumar SS, Stroup DF, Laredo SE. The association between the combined oral contraceptive pill and insulin resistance, dysglycemia and dyslipidemia in women with polycystic ovary syndrome: a systematic review and meta-analysis of observational studies. Hum Reprod 2011;26(1):191-201. [URL]

Weight control in polycystic ovary syndrome

Weight control in polycystic ovary syndrome

Many individuals with polycystic ovary syndrome (PCOS) are overweight (have a body mass index [BMI] between 25 to 29 kg/m^2), obese (BMI of 30 kg/m^2 or more) or centrally obese. Obesity in individuals with PCOS increases the risk and severity of:

- menstrual disturbance
- infertility
- obstructive sleep apnoea
- insulin resistance and type 2 diabetes
- cardiovascular disease
- poor mental health
- nonalcoholic fatty liver disease.

In overweight individuals with PCOS, losing 5% of total body weight results in:

- reduced insulin resistance and hyperandrogenism
- improved ovulatory function, fertility and psychological wellbeing.

Losing 5% of total body weight improves metabolic, reproductive and mental health in individuals with PCOS.

For information on weight management, see General principles of management of excess body weight.

If lifestyle measures are not effective in managing weight after 6 months, consider adding metformin. Metformin does not cause significant weight loss but may prevent weight gain.

Consider metformin as an adjunct to lifestyle measures in weight management for individuals with PCOS.

Insulin resistance, impaired glucose tolerance and type 2 diabetes in polycystic ovary syndrome

Insulin resistance, impaired glucose tolerance and type 2 diabetes in polycystic ovary syndrome

Polycystic ovary syndrome (PCOS) is often associated with insulin resistance. Consequences of insulin resistance include:

- exacerbation of ovarian androgen overproduction and suppression of sex hormone–binding globulin (SHBG), leading to increased bioavailability of androgens
- development of impaired glucose tolerance or type 2 diabetes; risk is increased several-fold compared to individuals without PCOS.

Individuals with PCOS at **high risk of type 2 diabetes** include those with:

- a body mass index (BMI) higher than 25 kg/m^2 for Caucasians or 23 kg/m^2 for Asians
- an impaired fasting serum glucose concentration
- impaired glucose tolerance
- a family history of diabetes
- a history of gestational diabetes
- hypertension
- high-risk ethnicity (eg Africans, Aboriginal and Torres Strait Islander peoples, and South East Asians).

Screen all individuals with PCOS using fasting blood glucose, HbA1c or an oral glucose tolerance test (OGTT), and repeat every 1 to 3 years. Initial screening with an OGTT is preferred in individuals with PCOS who are at high risk of type 2 diabetes, or who are contemplating pregnancy, because it is the most sensitive test.

Screen all individuals with PCOS for abnormalities of glucose metabolism every 1 to 3 years.

Dietary and exercise measures, as outlined for weight management, can improve insulin sensitivity and reduce the risk of developing type 2 diabetes. Although studies in individuals with PCOS are lacking, studies in other populations suggest exercise may reduce insulin resistance in the absence of weight loss.

Metformin is recommended for individuals at high risk of developing type 2 diabetes, even if current tests of glucose metabolism are normal. Metformin has also been shown to counter other sequelae of insulin resistance in PCOS (ovarian androgen overproduction and suppression of SHBG). For information on the role of metformin in PCOS, see here.

If an individual with PCOS is diagnosed with type 2 diabetes, see Metformin for adults with type 2 diabetes.

For further details on screening and management of insulin resistance, see the International evidence-based guideline for the assessment and management of polycystic ovary syndrome and the PCOS Practice Tools for Health Practitioners.

Cardiovascular risk in polycystic ovary syndrome

Cardiovascular risk in polycystic ovary syndrome

Individuals with polycystic ovary syndrome (PCOS) usually have risk factors for cardiovascular disease, such as excess weight, abnormal glucose metabolism or dyslipidaemia (low high-density lipoprotein cholesterol [HDL-C], high triglycerides); however, an increase in cardiovascular mortality in individuals with PCOS has not been conclusively proven.

Assess cardiovascular risk factors in all individuals with PCOS.

Assess absolute cardiovascular risk in all individuals with PCOS, and treat accordingly. See also the International evidence-based guideline for the assessment and management of polycystic ovary syndrome and the PCOS Practice Tools for Health Practitioners .

Mental health in polycystic ovary syndrome

Mental health in polycystic ovary syndrome

Polycystic ovary syndrome (PCOS) has symptoms and long-term implications for health that may lead to decreased quality of life and psychological morbidity. Assess psychological wellbeing in all individuals with PCOS and consider referral to a mental health professional.

Assess psychological wellbeing in all individuals with PCOS.

Weight gain and hirsutism are the most frequently reported concerns associated with psychological morbidity; the risks of poor body image, eating disorders and sexual difficulties are increased. For further information, see the International evidence-based guideline for the assessment and management of polycystic ovary syndrome and the PCOS Practice Tools for Health Practitioners .

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Consider the possibility of PCOS in females presenting with menstrual disturbance, hirsutism or premenopausal alopecia. Acne is less strongly associated with PCOS, but PCOS should be considered if hirsutism, alopecia, menstrual disturbance or obesity are also present. Before confirming a diagnosis of PCOS, exclude other causes of presenting features.

Diagnosis of PCOS requires exclusion of differential diagnoses.

A diagnosis is made if an adult meets **two of the following diagnostic criteria** and other causes have been excluded:

- menstrual disturbance, including secondary oligomenorrhoea or amenorrhoea
- clinical or biochemical hyperandrogenism
- polycystic appearance of ovaries on ultrasound.

Additional features of PCOS (which are not essential for diagnosis) include:

- obesity
- insulin resistance (with a tendency to develop type 2 diabetes)
- subfertility

An ultrasound scan is not required for the diagnosis of PCOS if an adult has both menstrual disturbance and clinical or biochemical hyperandrogenism. If only one of these features is present, a transvaginal ultrasound should be performed in the first half of the menstrual cycle, and a follicle count should be requested [Note 1].

PCOS can be diagnosed without ultrasound if an adult has both menstrual disturbance and clinical or biochemical hyperandrogenism.

Refer adolescents with suspected PCOS for specialist assessment because interpretation of clinical features and ultrasound findings in adolescence is complex. Menstrual irregularity is only considered abnormal if it persists for more than 2 years post menarche. Normal adolescent ovaries may have a polycystic appearance for up to 8 years, so ultrasound is not recommended.

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- insulin resistance
  - exacerbation of hyperandrogenism
  - increased risk of type 2 diabetes and cardiovascular disease
- additional cardiovascular risk factors such as dyslipidaemia
- poor mental health (in particular, body-image concerns related to excess weight and hirsutism).

Most aspects of PCOS can be managed in general practice, but specialist referral is appropriate if:

- diagnosis is uncertain (eg in adolescents)
- hirsutism is not responding to antiandrogen therapy after 6 to 12 months
- seeking fertility treatment.

For more detailed information on the management of PCOS, see the International evidence-based guideline for the assessment and management of polycystic ovary syndrome and the PCOS Practice Tools for Health Practitioners.

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Metformin also **suppresses ovarian androgen production**, which improves the frequency of ovulation in individuals with PCOS. Although it is not recommended for managing irregular bleeding, it can be used in managing subfertility.

If metformin is indicated, use:

1 metformin immediate-release 500 mg orally, daily with evening meal as an initial dose; increase daily dose by 500 mg every 1 to 2 weeks as tolerated, up to a maximum of 1500 mg daily in 2 or 3 divided doses
polycystic ovary syndrome

OR

2 metformin modified-release 500 mg orally, daily with evening meal as an initial dose; increase daily dose by 500 mg every 1 to 2 weeks as tolerated, up to a maximum of 1500 mg daily.

Most studies of metformin for PCOS used immediate-release metformin. Gastrointestinal effects of immediate-release metformin can be minimised by starting treatment at a low dose, titrating gradually, and taking with food. If this is not tolerated, modified-release metformin may be used.

If type 2 diabetes is diagnosed in an individual with PCOS, see Metformin for adults with type 2 diabetes for information on metformin dosage, mode of action and adverse effects.

Menstrual disturbance and polycystic ovary syndrome

Menstrual disturbance and polycystic ovary syndrome

Overview of menstrual disturbance and polycystic ovary syndrome

Overview of menstrual disturbance and polycystic ovary syndrome

Many individuals with polycystic ovary syndrome (PCOS) have anovulatory cycles resulting in menstrual disturbance, including:

- irregular menstrual cycles of unusual length or variability
- oligomenorrhoea or amenorrhoea

Prolonged estrogenic stimulation of the endometrium during anovulatory cycles, without progestogen-induced shedding, causes endometrial thickening. This can result in heavy bleeding when menstruation does occur, and increases the risk of endometrial cancer 2-to 6-fold. Fertility is reduced in individuals with PCOS who have menstrual disturbance, but conception can occur even if menstruation occurs only occasionally; see PCOS and subfertility.

In those not wishing to conceive, menstrual regulation aims to control bleeding and provide protection from estrogen-induced endometrial cancer. Investigate heavy menstrual bleeding that persists despite 6 months of therapy to exclude endometrial cancer. Investigate earlier if there are additional features that increase cancer risk.

Treatment of menstrual disturbance in individuals with polycystic ovary syndrome

Treatment of menstrual disturbance in individuals with polycystic ovary syndrome

Combined oral contraceptives (COCs) provide the most effective menstrual regulation in PCOS; they also provide effective contraception. They have the added benefit of suppressing ovarian androgen production, which can be beneficial for hirsutism, acne and androgenetic alopecia. Although some small studies of COCs have shown an adverse effect on glucose metabolism, a meta-analysis did not find that they worsen insulin resistance in individuals with PCOS [Note 2].

Combined oral contraceptives provide the most effective menstrual regulation in PCOS.

Although COCs containing antiandrogenic progestogens (eg cyproterone dienogest, drospirenone) may have added benefit compared to formulations with other progestogens, there are limited head-to-head comparisons and insufficient data to recommend specific formulations.

Use the lowest dose of estrogen that effectively controls the menstrual cycle. Use:

combined oral contraceptive orally, once daily (see Table 20.12 for formulations). Advise extended or continuous use to avoid or minimise withdrawal bleeding. *polycystic ovary syndrome*

If COCs are contraindicated, the 52 mg levonorgestrel-releasing intrauterine contraceptive device (LNG-IUD) can be used to provide endometrial protection and contraception. Use:

levonorgestrel-releasing IUD 52 mg inserted into the uterus. Replace every 5 years. *polycystic ovary syndrome*

An **oral cyclical progestogen** can be considered for individuals who have a contraindication or preference to avoid COCs or the LNG-IUD. Oral cyclical progestogens induce endometrial shedding and provide endometrial protection; however, they should not be used long term because they:

- are less effective than the LNG-IUD for regulating menstruation
- do not address other aspects of PCOS such as hyperandrogenism
- are poorly tolerated (adverse effects include breast tenderness and headaches)
- confer a risk of hypoestrogenism (which affects bone health and possibly cardiovascular health).

If an oral cyclical progestogen is indicated, see Heavy menstrual bleeding for dosages.
Oral cyclical progestogens provide only short-term treatment for menstrual disturbance in PCOS.

Metformin may increase menstrual frequency in individuals with PCOS by inducing ovulation. However, metformin is not recommended for management of menstrual disturbance in individuals with PCOS (except to treat impaired fertility); it provides poor control of heavy bleeding and inadequate protection against endometrial hyperplasia and cancer.

Metformin is not recommended for management of menstrual disturbance in PCOS other than as part of treatment for subfertility.

Note 2: Halperin IJ, Kumar SS, Stroup DF, Laredo SE. The association between the combined oral contraceptive pill and insulin resistance, dysglycemia and dyslipidemia in women with polycystic ovary syndrome: a systematic review and meta-analysis of observational studies. Hum Reprod 2011;26(1):191-201. [URL]

Weight control in polycystic ovary syndrome

Weight control in polycystic ovary syndrome

Many individuals with polycystic ovary syndrome (PCOS) are overweight (have a body mass index [BMI] between 25 to 29 kg/m^2), obese (BMI of 30 kg/m^2 or more) or centrally obese. Obesity in individuals with PCOS increases the risk and severity of:

- menstrual disturbance
- infertility
- obstructive sleep apnoea
- insulin resistance and type 2 diabetes
- cardiovascular disease
- poor mental health
- nonalcoholic fatty liver disease.

In overweight individuals with PCOS, losing 5% of total body weight results in:

- reduced insulin resistance and hyperandrogenism
- improved ovulatory function, fertility and psychological wellbeing.

Losing 5% of total body weight improves metabolic, reproductive and mental health in individuals with PCOS.

For information on weight management, see General principles of management of excess body weight.

If lifestyle measures are not effective in managing weight after 6 months, consider adding metformin. Metformin does not cause significant weight loss but may prevent weight gain.

Consider metformin as an adjunct to lifestyle measures in weight management for individuals with PCOS.

Insulin resistance, impaired glucose tolerance and type 2 diabetes in polycystic ovary syndrome

Insulin resistance, impaired glucose tolerance and type 2 diabetes in polycystic ovary syndrome

Polycystic ovary syndrome (PCOS) is often associated with insulin resistance. Consequences of insulin resistance include:

- exacerbation of ovarian androgen overproduction and suppression of sex hormone–binding globulin (SHBG), leading to increased bioavailability of androgens
- development of impaired glucose tolerance or type 2 diabetes; risk is increased several-fold compared to individuals without PCOS.

Individuals with PCOS at **high risk of type 2 diabetes** include those with:

- a body mass index (BMI) higher than 25 kg/m^2 for Caucasians or 23 kg/m^2 for Asians
- an impaired fasting serum glucose concentration
- impaired glucose tolerance
- a family history of diabetes
- a history of gestational diabetes
- hypertension
- high-risk ethnicity (eg Africans, Aboriginal and Torres Strait Islander peoples, and South East Asians).

Screen all individuals with PCOS using fasting blood glucose, HbA1c or an oral glucose tolerance test (OGTT), and repeat every 1 to 3 years. Initial screening with an OGTT is preferred in individuals with PCOS who are at high risk of type 2 diabetes, or who are contemplating pregnancy, because it is the most sensitive test.

Screen all individuals with PCOS for abnormalities of glucose metabolism every 1 to 3 years.

Dietary and exercise measures, as outlined for weight management, can improve insulin sensitivity and reduce the risk of developing type 2 diabetes. Although studies in individuals with PCOS are lacking, studies in other populations suggest exercise may reduce insulin resistance in the absence of weight loss.

Metformin is recommended for individuals at high risk of developing type 2 diabetes, even if current tests of glucose metabolism are normal. Metformin has also been shown to counter other sequelae of insulin resistance in PCOS (ovarian androgen overproduction and suppression of SHBG). For information on the role of metformin in PCOS, see here.

If an individual with PCOS is diagnosed with type 2 diabetes, see Metformin for adults with type 2 diabetes.

For further details on screening and management of insulin resistance, see the International evidence-based guideline for the assessment and management of polycystic ovary syndrome and the PCOS Practice Tools for Health Practitioners.

Cardiovascular risk in polycystic ovary syndrome

Cardiovascular risk in polycystic ovary syndrome

Individuals with polycystic ovary syndrome (PCOS) usually have risk factors for cardiovascular disease, such as excess weight, abnormal glucose metabolism or dyslipidaemia (low high-density lipoprotein cholesterol [HDL-C], high triglycerides); however, an increase in cardiovascular mortality in individuals with PCOS has not been conclusively proven.

Assess cardiovascular risk factors in all individuals with PCOS.

Assess absolute cardiovascular risk in all individuals with PCOS, and treat accordingly. See also the International evidence-based guideline for the assessment and management of polycystic ovary syndrome and the PCOS Practice Tools for Health Practitioners .

Mental health in polycystic ovary syndrome

Mental health in polycystic ovary syndrome

Polycystic ovary syndrome (PCOS) has symptoms and long-term implications for health that may lead to decreased quality of life and psychological morbidity. Assess psychological wellbeing in all individuals with PCOS and consider referral to a mental health professional.

Assess psychological wellbeing in all individuals with PCOS.

Weight gain and hirsutism are the most frequently reported concerns associated with psychological morbidity; the risks of poor body image, eating disorders and sexual difficulties are increased. For further information, see the International evidence-based guideline for the assessment and management of polycystic ovary syndrome and the PCOS Practice Tools for Health Practitioners .

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[X] Close

Definition of male androgen deficiency

Definition of male androgen deficiency

This topic covers management of androgen deficiency in cis men; for advice on gender-affirming hormone therapy and gender-inclusive primary healthcare, see resources for trans and gender diverse health care. For information on androgen deficiency in childhood, see Delayed puberty in males.

Male androgen deficiency is defined as impaired testosterone production (due to proven dysfunction in the hypothalamic–pituitary–testicular [HPT] axis) that causes symptoms or effects on target organs.

Male hypogonadism is male androgen deficiency accompanied by impaired fertility; it may be:

- **hypergonadotrophic**—caused by primary (testicular) disorders that reduce testosterone production and spermatogenesis; these, in turn, reduce negative feedback on gonadotrophin (luteinising hormone [LH] and follicle stimulating hormone [FSH]) production, leading to increased gonadotrophin concentrations
- **hypogonadotrophic**—caused by a central (hypothalamic or pituitary) disorder that reduces production of gonadotrophins, diminishing stimuli to the testis to produce hormones and sperm.

For treatment of infertility in male hypogonadism, see Gonadotrophin therapy for male infertility.

Causes of male androgen deficiency

Causes of male androgen deficiency

Primary male androgen deficiency causes symptoms or signs of androgen deficiency, low serum testosterone concentration and elevated serum luteinising hormone (LH) concentration. It results from testicular disorders, including:

- Klinefelter syndrome [Note 1]
- cryptorchidism
- orchidectomy
- orchitis
- cytotoxic or radiation damage to the testes
- testicular torsion or trauma
- androgen synthesis inhibitors.

Central androgen deficiency causes symptoms or signs of androgen deficiency and low serum testosterone and LH concentrations. It results from hypothalamic or pituitary disorders, including hyperprolactinaemia.

- pituitary tumours
- pituitary surgery or radiotherapy
- haemochromatosis, which can cause iron deposition in the hypothalamus and pituitary
- hypophysitis
- idiopathic hypogonadotrophic hypogonadism (including Kallmann syndrome, notable for reduced or absent sense of smell [Note 2]
- gonadotrophin-releasing hormone (GnRH) analogues.

Conditions to be distinguished from central androgen deficiency include:

- exogenous synthetic androgen use

- recent acute illness and convalescence
- functionally low testosterone concentrations.

Use of **exogenous synthetic androgens** may result in a biochemical picture that is similar to central androgen deficiency, but without the expected clinical signs of androgen deficiency; see History and examination.

Recent acute illness and convalescence can cause temporary hypothalamic–pituitary–testicular axis suppression.

Also consider the possibility of functionally low serum testosterone concentration , in which total serum testosterone concentration is usually only mildly reduced in men with comorbidities.

Note 1: For information on Klinefelter syndrome, see the US National Library of Medicine Medline Plus website.

Note 2: For information on Kallmann syndrome, see the US National Library of Medicine Medline Plus website

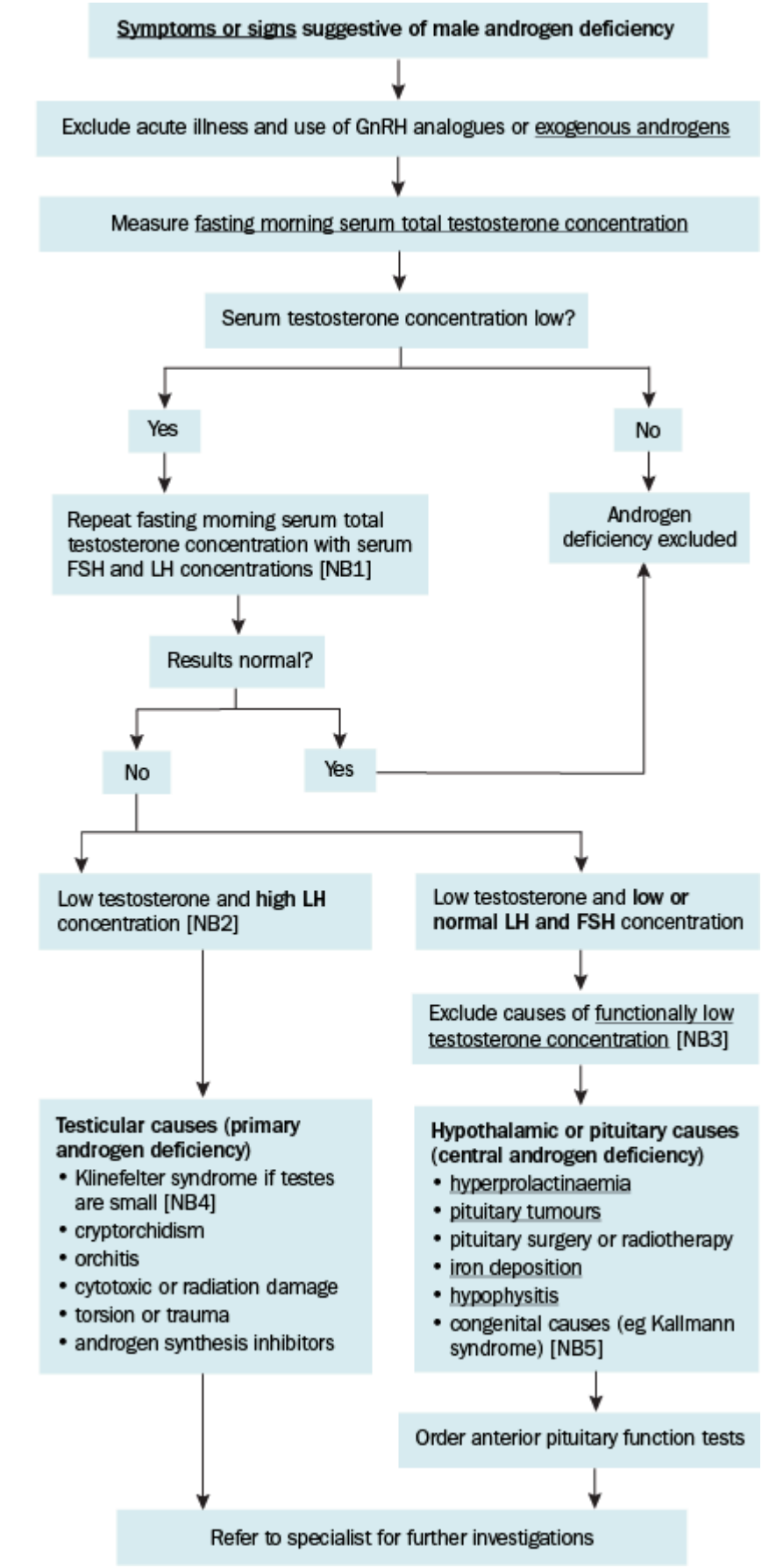
Overview of diagnosis of male androgen deficiency

Overview of diagnosis of male androgen deficiency

Figure 20.14 outlines an approach to diagnosis in suspected androgen deficiency. The aims are to:

- determine whether criteria for androgen deficiency are met
- exclude differential diagnoses
- undertake initial investigations to seek the cause of androgen deficiency (if feasible) before referral.

Figure 20.14 Approach to diagnosis in suspected male androgen deficiency



FSH = follicle stimulating hormone; GnRH = gonadotrophin-releasing hormone; LH = luteinising hormone

NB1: Serum FSH concentration may be easier to interpret than LH, as LH is pulsatile. Serum FSH concentration is also part of assessment for male infertility, which can accompany some causes of androgen deficiency.

NB2: Low testosterone and slightly elevated LH concentrations may be due to normal ageing; see Interpreting serum testosterone concentrations..

NB3: Mildly low testosterone and normal LH concentrations may be due to comorbidities such as obesity, diabetes, depression, or use of opioids, high-dose corticosteroids, alcohol or marijuana; see Interpreting serum testosterone concentrations.

NB4: For information on Klinefelter syndrome, see the US National Library of Medicine Medline Plus website.

NB5: For information on Kallmann syndrome, see the US National Library of Medicine Medline Plus website.

History and examination in male androgen deficiency

History and examination in male androgen deficiency

Androgen deficiency should not be diagnosed unless symptoms and signs are found on history and examination. Many symptoms of androgen deficiency are nonspecific.

Symptoms and signs most likely to indicate androgen deficiency include reduced libido, decreased spontaneous erections, hot flushes, reduced facial hair growth, breast discomfort or gynaecomastia, loss of axillary and pubic hair, small testes (especially volume under 5 mL, assessed using an orchidometer) and low bone mass (particularly low Z-scores). Very small testes are a feature of Klinefelter syndrome [Note 3], which is often missed unless a testicular examination is performed.

Examine men with suspected androgen deficiency for small testes.

Less specific symptoms and signs of androgen deficiency include decreased energy, motivation, concentration, memory or work performance; low mood; disturbed sleep or increased sleepiness; reduced muscle bulk and strength; increased body fat or body mass index; and mild anaemia. Many of these features may be seen with different diagnoses associated with low serum testosterone, such as:

- functionally low serum testosterone concentration
- acute illness.

Rather than typical signs of androgen deficiency (although testicular shrinkage is a feature), use of exogenous androgenic steroids may cause truncal acne and marked muscular development. Ask directly about the use of exogenous synthetic androgens (including unregulated supplements, which may contain unrecognised ingredients).

Ask directly about the use of exogenous androgens, including the use of unregulated supplements.

Note 3: For information on Klinefelter syndrome, see the US National Library of Medicine Medline Plus website.

Interpreting serum testosterone concentrations in diagnosis of male androgen deficiency

Interpreting serum testosterone concentrations in diagnosis of male androgen deficiency

A low serum testosterone concentration must be interpreted in the context of the man's clinical features. For a diagnosis, the following **criteria for diagnosing male androgen deficiency** must all be met:

- symptoms or signs are consistent with male androgen deficiency
- unequivocally low fasting early morning total serum testosterone concentration, confirmed by repeat measurement on a different day

- hypothalamic–pituitary–testicular (HPT) axis dysfunction confirmed.

Serum testosterone concentrations have a wide diurnal variation and are highest in the morning. Samples must be taken between 8 am and 10 am [Note 4], after overnight fasting and confirmed by a repeat measurement on a different day.
Low serum testosterone concentration must be confirmed by repeating the measurement.

Systemic illness temporarily lowers testosterone concentrations and can confound assessment of symptoms. Testosterone should not be measured during an acute illness or convalescence.

Do not measure serum testosterone concentration during an acute illness or convalescence.

Reference ranges for total serum testosterone concentration vary because of factors such as assay method and age. Published ranges relate to mass spectrometry but at the time of writing most laboratories in Australia use immunoassays, so in practice, local reference ranges are used [Note 5].

Some conditions, such as obesity, diabetes and depression, and use of opioids or glucocorticoids, cause a mild reduction in total serum testosterone concentration that does not amount to androgen deficiency, and is generally managed by treating the underlying condition. This finding is referred to as **functionally low total serum testosterone concentration**. Serum gonadotrophin (luteinising hormone [LH] and follicle stimulating hormone [FSH]) concentrations are usually normal; this is consistent with mild functional central suppression of the HPT axis. The underlying conditions may also cause:

- confounding symptoms that overlap with those of androgen deficiency (particularly the less specific features) but are not usually a result of the low testosterone concentration
- reduced hepatic synthesis of sex hormone–binding globulin ([SHBG], the main protein that binds testosterone)—particularly in men with obesity, insulin resistance or glucocorticoid use. This can reduce the total serum testosterone concentration without necessarily affecting the amount of unbound (free) testosterone or having a clinical impact.

Some laboratories report **free serum testosterone concentrations** (calculated using the total serum testosterone and SHBG concentrations). Neither calculations nor reference ranges for free serum testosterone are established. A low free serum testosterone concentration (without a low total serum testosterone concentration) does not warrant testosterone therapy because evidence of clinical benefit is lacking.

If there is uncertainty about the interpretation of serum testosterone concentrations, seek specialist advice.

Note 4: For shift workers or sleep-deprived men, measure testosterone shortly after waking.

Note 5: When assayed by mass spectrometry (not immunoassay which is used by most laboratories), the lower limit for total serum testosterone in males aged 21 to 35 years with normal sexual and reproductive function is 10.4 nanomol/L and in healthy males aged 70 to 89 years is 6.4 nanomol/L. Reference ranges using mass spectrometry are less well defined for males aged 35 to 70 years.

Approach to testosterone replacement therapy

Approach to testosterone replacement therapy

Before considering testosterone replacement therapy, perform assessment as outlined in Figure 20.14 to determine whether criteria for a diagnosis of male androgen deficiency are met.

If criteria are not met but functionally low serum testosterone concentration is suspected, consider whether correction of underlying causes is possible. Management should focus initially on lifestyle measures, particularly weight loss where relevant, and treating comorbidities. Australian management guidelines recommend against testosterone therapy for functionally low serum testosterone concentration. The T-Trials [Note 6] enrolled males with functionally low serum testosterone concentrations and at least one of the following problems: decreased libido, difficulty walking, or low vitality. Testosterone treatment modestly

improved sexual function in those with low libido, walking distance in men with difficulty walking, haemoglobin concentration, and lumbar spine bone mineral density, but questions remain about cardiovascular safety, and long-term clinical outcomes.

Consider referral to an endocrinologist for management of functionally low serum testosterone concentration.

If criteria for diagnosing androgen deficiency are met, investigate causes as outlined in Figure 20.14, if feasible, or refer for investigation and management.
The pathological basis of androgen deficiency should be fully investigated before starting testosterone replacement therapy.

Testosterone replacement aims to relieve the symptoms and signs of androgen deficiency. It is not indicated for treatment of low libido or erectile dysfunction in males who are not androgen deficient. The Pharmaceutical Benefits Scheme criteria for prescribing of testosterone for androgen deficiency are stringent; specialist referral is required. Testosterone replacement suppresses spermatogenesis, so referral to a fertility specialist may be required before starting replacement.

Consider referral to discuss fertility options before starting testosterone replacement therapy.

Androgen deficiency may recover if a reversible cause is treated (eg hyperprolactinaemia is corrected with a dopamine agonist). Androgen deficiency caused by an irreversible disorder requires lifelong testosterone replacement therapy.

Testosterone therapy is contraindicated in males with current prostate or breast cancer, those desiring fertility, and elite athletes (because it is a prohibited substance). For males who have had curative treatment for breast or prostate cancer, specialist assessment of harms and benefits of testosterone therapy is required.

Monitoring of testosterone replacement therapy is advised to assess efficacy and detect adverse effects.

Note 6: Snyder PJ, Bhasin S, Cunningham GR, Matsumoto AM, Stephens-Shields AJ, Cauley JA, et al. Effects of testosterone treatment in older men. N Engl J Med 2016;374(7):611-24. [URL]

Testosterone formulations for replacement therapy

Testosterone formulations for replacement therapy

Overview of testosterone formulations

Overview of testosterone formulations

Testosterone replacement therapy for male androgen deficiency can be undertaken with transdermal, injectable or oral testosterone formulations. The choice of formulation is guided by effectiveness, patient preference, convenience and adverse effects.

Transdermal formulations of testosterone may be preferred over intramuscular formulations if the man wishes to avoid injections, has a bleeding disorder or is taking anticoagulants.

Testosterone injections may be more convenient than daily application of transdermal formulations.

Oral testosterone therapy is less effective than other formulations and is rarely used.

Transdermal testosterone replacement therapy

Transdermal testosterone replacement therapy

For transdermal testosterone replacement therapy, use:

1 testosterone 5% cream 2 mL (100 mg) transdermally, in the morning applied to the trunk or proximally on the limbs. Adjust in 1 mL (50 mg) increments according to clinical response and serum testosterone concentration. Maximum dose 4 mL (200 mg) daily *male androgen deficiency, topical therapy*

OR

1 testosterone 1% gel 5 g (50 mg) transdermally, in the morning applied to the trunk or proximally on the limbs. Adjust in 2.5 g (25 mg) increments according to clinical response and serum testosterone concentration. Maximum dose 10 g (100 mg) daily [Note 7]

OR

1 testosterone 2% gel 1 pump (23 mg/1.15 g) transdermally, in the morning applied to trunk or proximally on the limbs. Adjust in 1 pump (23 mg) increments according to clinical response and serum testosterone concentration. Maximum dose 3 pumps (69 mg/3.45 g) daily

OR

2 testosterone patch 5 mg per 24 hours transdermally, at night applied to the trunk or proximally on the limbs for 24 hours. Adjust in 2.5 mg per 24 hours increments according to clinical response and serum testosterone concentration. Maximum dose 7.5 mg per 24 hours.

See Monitoring testosterone replacement therapy for guidance on adjusting testosterone therapy.

The main limitation of transdermal testosterone patches is skin irritation, which is occurs in about 50% of patients and can be severe. Pretreating the application site with topical hydrocortisone may reduce irritation.

To avoid transferring active drug to another person through skin-to-skin contact, advise thorough hand washing after applying testosterone gel or liquid, covering the application area with clothing, and showering before direct skin contact with others. Repeated inadvertent transfer to another person could increase their serum testosterone concentration and cause adverse effects (eg growth of facial or body hair, deepening of the voice, menstrual irregularities in females, premature puberty and genital enlargement in children).

Note 7: Testosterone 1% gel is available in 25 mg and 50 mg sachets, and in a pump dispensing 12.5 mg per actuation.

Intramuscular testosterone replacement therapy

Intramuscular testosterone replacement therapy

Testosterone injection must be given by deep intramuscular injection; it is not recommended in individuals with bleeding disorders or those receiving anticoagulation. Give the injection very slowly to minimise discomfort, and take care to avoid inadvertent intravenous administration.

For intramuscular testosterone replacement therapy, use:

1 testosterone undecanoate 1000 mg by deep intramuscular injection; repeat after 6 weeks and then every 10 to 14 weeks, according to clinical response and serum testosterone concentration. For more gradual replacement, give the second dose after 10 to 14 weeks *male androgen deficiency, intramuscular therapy*

OR

2 testosterone enantate 250 mg by deep intramuscular injection, every 2 to 3 weeks

OR

2 testosterone esters 250 mg by deep intramuscular injection, every 2 to 3 weeks.

See Monitoring testosterone replacement therapy for guidance on adjusting testosterone therapy.

Although uncommon, coughing, dyspnoea, sweating, chest pain, dizziness, paraesthesia, or syncope can occur during or immediately after injection of testosterone. This has been attributed to pulmonary oil microembolism. Treatment is supportive, and further therapy with intramuscular testosterone is not contraindicated.

Testosterone enantate or testosterone ester injections may be associated with marked fluctuation in testosterone concentration, leading to variation in energy, wellbeing and libido.

Oral testosterone replacement therapy

Oral testosterone replacement therapy

Oral testosterone undecanoate is less effective than other testosterone formulations. It has low (under 10%) and variable bioavailability and a short duration of action, so multiple daily doses are required.

For oral testosterone replacement therapy, use:

testosterone undecanoate 120 to 160 mg orally, daily in 2 divided doses for 2 to 3 weeks. Adjust dose according to clinical response and serum testosterone concentration (usual range 80 mg to 240 mg daily). *male androgen deficiency, oral therapy* _

See Monitoring testosterone replacement therapy for guidance on adjusting testosterone therapy.

Monitoring testosterone replacement therapy

Monitoring testosterone replacement therapy

Overview of monitoring testosterone replacement therapy

Overview of monitoring testosterone replacement therapy

Monitoring testosterone replacement therapy for male androgen deficiency involves reviewing response to therapy (by assessing clinical response and measuring testosterone concentration) and being alert to evidence of adverse events. See Table 20.34 for a summary of monitoring undertaken by a specialist or under specialist guidance.

Table 20.34 Monitoring for clinical response and serious adverse effects of testosterone replacement therapy

Reason for monitoring	Action
	review improvement in symptoms of male androgen deficiency 3 months after starting testosterone, then at least annually
assessing adequacy of testosterone replacement	measure serum testosterone concentration 3 to 6 months after starting testosterone, then as determined by response
	measure bone mineral density 12 months or more after starting testosterone
risk of polycythaemia	review FBE at baseline, 3 months after starting testosterone, then at least annually
	assess baseline risk of prostate cancer
risk of promoting growth in a pre-existing prostate cancer [NB1]	exclude symptoms of prostate cancer
	discuss limitations of PSA screening with asymptomatic men; if PSA screening is chosen, see here for advice on frequency of monitoring
cardiovascular risk in frail older men [NB2]	assess baseline cardiovascular risk factors; review for symptoms of fluid overload

Reason for monitoring	Action

- FBE = full blood examination; PSA = prostate specific antigen
- NB1: For discussion of testosterone replacement therapy and prostate cancer risk, see Monitoring for adverse effects of testosterone replacement therapy.
- NB2: Data on cardiovascular risks of testosterone replacement therapy are conflicting; see Monitoring for adverse effects of testosterone replacement therapy.

Monitoring response to testosterone replacement therapy

Monitoring response to testosterone replacement therapy

Most **symptoms and signs** of androgen deficiency respond within 1 to 2 months of starting treatment. Libido is expected to increase; this may be experienced as either a benefit or an adverse effect by men or their partners. Changes in body composition can occur within 3 to 6 months. Assess bone mineral density every 12 months or more to check that the testosterone dose is adequate for bone maintenance.

Measure **serum total testosterone concentration** 3 to 6 months after starting testosterone, then at intervals determined by clinical response and whether dose modification has been required. If testing is required after a change in dose, it should be performed after at least 2 weeks. Target total testosterone concentrations are in the lower half of the reference range. Timing of measurements depends on the testosterone formulation used:

- for **cream**, measure in the morning predose
- for **1% transdermal gel**, measure in the morning predose
- for **2% transdermal gel**, measure 2 to 4 hours after dose
- for **patches**, measure 3 to 12 hours after application
- for **intramuscular testosterone undecanoate**, measure in the morning just before the third dose after a dose change
- for **short-acting injectable formulations** (testosterone enantate and esters), measure in the morning midway between injections.

Multiple-daily dosing with oral testosterone is not readily monitored with serum testosterone concentrations.

Monitoring for adverse effects of testosterone replacement therapy

Monitoring for adverse effects of testosterone replacement therapy

Adverse testosterone effects include common effects (which can be mild and reversible) or more serious effects, for which monitoring is needed. Table 20.34 includes a summary of monitoring for adverse events.

Common adverse effects from testosterone replacement therapy include truncal seborrhoea and acne (particularly with testosterone ester injections), modest weight gain (under 3 kg) and reduced spermatogenesis. Increased truncal hair, temporal hair loss or balding, and gynaecomastia can also occur. Adverse effects generally reverse when therapy is stopped.

Serious adverse effects from testosterone replacement therapy are uncommon but include polycythaemia, prostate growth, and transient worsening of obstructive sleep apnoea. Risk of cardiovascular events and venous thromboembolism may be increased in men taking testosterone, but evidence to confirm this association is lacking.

Polycythaemia occurs most often with short-acting injectable testosterone (esters and enantate forms). Measure haemoglobin and haematocrit at baseline, then 3 months after starting therapy, then annually. Exclude other causes of secondary polycythaemia (including smoking, obstructive sleep apnoea, and respiratory failure). Polycythaemia is treated by interrupting therapy, dose reduction or increasing the dose interval. Occasionally, venesection is required.

Testosterone therapy reverses the reduced prostate volume and prostate specific antigen (PSA) concentration that occur in male androgen deficiency. This **prostate growth** can lead to elevated prostate specific antigen

(PSA), which, if monitored, may prompt investigation for prostate cancer. There is no association between testosterone replacement and incident prostate cancer, except that men with lifelong untreated androgen deficiency are at reduced risk.

For individuals at substantial risk of pre-existing prostate cancer, measure PSA before starting testosterone therapy. If warranted by symptoms, perform digital rectal examination, or refer for urological assessment. Prostate cancer risk may be increased if any of the following are present:

- prostatic symptoms
- a strong family history [Note 8]
- previous serum PSA concentration more than 4 nanogram/mL.

For asymptomatic men, PSA testing before or during testosterone replacement constitutes prostate cancer screening. Given there is no consensus about population screening for prostate cancer, this issue should be addressed by the testosterone prescriber according to existing guidelines, which support discussing screening in males aged 50 to 69 years at average risk using a decision aid [Note 9].

If prostate screening and monitoring is chosen, at the time of writing, guidelines suggest measuring PSA at baseline, then 3 to 12 months after starting testosterone therapy, then every 2 years.

Risk of **cardiovascular events** may be increased in frail older men taking testosterone, although the evidence for an effect of testosterone is mixed and the association is unconfirmed. The T-Trials cardiovascular trial [Note 10] observed a greater 12-month increase in the primary endpoint, noncalcified coronary plaque volume, in testosterone-treated males, but the clinical relevance of this remains undefined. Assess cardiovascular risk before starting testosterone therapy and manage risk factors as for the general population. Closely monitor older people (particularly those with frailty) and those with cardiovascular disease, kidney failure or severe hypertension. Testosterone therapy can cause fluid overload from sodium and fluid retention, which can exacerbate these conditions.

Note 8: For advice on familial prostate cancer risk, see the Royal Australian College of General Practitioners (RACGP) guideline Genomics in general practice.

Note 9: See the Royal Australian College of General Practitioners (RACGP) guideline on prostate cancer screening.

Note 10: Budoff MJ, Ellenberg SS, Lewis CE, Mohler ER, 3rd, Wenger NK, Bhasin S, et al. Testosterone treatment and coronary artery plaque volume in older males with low testosterone. JAMA 2017;317(7):708-16. [URL]

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Definition and causes of precocious puberty

Definition and causes of precocious puberty

Pubertal development is unusual in females younger than 8 years and males younger than 9 years. Precocious puberty (early onset of puberty) may be gonadotrophin-dependent (central) or gonadotrophin-independent.

Central precocious puberty is defined as breast development in females younger than 8 years and testicular enlargement in males younger than 9 years. It is caused by activation of the hypothalamic–pituitary axis; this is often idiopathic, but can be caused by brain lesions such as tumours, cysts or inflammatory conditions.

Gonadotrophin-independent precocious puberty is much less common. It can cause early pubertal changes that are in keeping with the child's primary sexual characteristics, but can also result in feminisation in males or virilisation in females. It arises from a range of conditions causing sex-hormone overproduction by the gonads or adrenal glands. These causes include ovarian cysts, ovarian tumours, testicular stromal and germ cell tumours; rare causes include severe primary hypothyroidism or genetic disorders such as McCune Albright syndrome [Note 1], testotoxicosis [Note 2] and congenital adrenal hyperplasia.

Precocious puberty is more common in females, in whom it is usually idiopathic, although specialist investigation to exclude a pathological cause must still be considered. In males, precocious puberty is more likely to have a pathological cause.

Precocious puberty is often confused with:

- **Premature adrenarche:** characterised by an early increase (before age 8 years) in adrenal androgens (eg dehydroepiandrosterone sulfate [DHEAS]), leading to acne, change in body odour and premature development of body hair, but no signs of central puberty (testicular development in males or breast development in females). This is the most common differential diagnosis of precocious puberty, especially in females.
- **Premature thelarche:** the early development of a small amount of breast tissue in females without a growth spurt or other pubertal signs. Breast tissue development before the age of 1 year is usually a normal variant, is common, and usually regresses. It requires specialist referral if it fails to regress, is progressive, is seen in females aged 2 years or older or if there are other concerns, such as rapid growth or other pubertal signs.

These two conditions require specialist referral, but unlike precocious puberty, the specialist assessment does not need to be undertaken urgently.

Premature adrenarche and premature thelarche should be distinguished from precocious puberty to determine the urgency of referral.

Note 1: For information on McCune Albright syndrome, see the US National Library of Medicine Medline Plus website.

Note 2: For information on testotoxicosis, see the Genetic and Rare Diseases Information Center.

Management of precocious puberty

Management of precocious puberty

Refer all children with precocious puberty for specialist evaluation; urgent assessment is required for males, as they are more likely to have a pathological cause. Urgent assessment is required for females if they have features suggestive of a pathological cause, such as persistent headaches, visual field changes, optic disc swelling, rapid progression of virilisation or very early onset puberty (before age 6 years).

Urgent specialist evaluation of precocious puberty is required for all males, and for females with features suggestive of a pathological cause.

Active treatment of precocious puberty is not always required and should only be started after specialist referral, assessment, and counselling of the child and their carer(s). The aims of treatment are to delay pubertal progress (eg delay menstruation in females) until an appropriate age and social stage, and to achieve optimal height.

Gonadotrophin-releasing hormone analogues, goserelin and leuprorelin, can be used to treat precocious puberty. A typical regimen is:

leuprorelin depot 30 mg by deep intramuscular injection, every 3 months. *precocious puberty* _

Gonadotrophin-releasing hormone analogues are not effective in children with gonadotrophin-independent precocious puberty (eg McCune Albright syndrome, testotoxicosis) unless the condition has triggered concurrent central puberty. Specialist referral is required. Gonadotrophin-releasing hormone analogues are also not recommended for normal (but early) puberty, especially if the primary goal of treatment is height augmentation (see also Short stature in children).

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