

# The role of the GP in managing male infertility

**A couple with subfertility should be assessed as a couple. However, there are certain aspects of management that apply only to the man. As with any other area of medicine, the medical history, examination and investigations are vital.**

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GPs are generally the first point of contact for couples having difficulty conceiving. Many GPs wonder if there is more they can do to help an infertile couple and at what point to refer them to a specialised clinic. This article outlines how GPs can assist couples with infertility prior to referral, and the tests and treatment options offered at specialist clinics.<sup>1</sup>

Infertility is thought to affect about one in six couples. For about 38% of these couples, the major problem is with the female partner, for 20% of couples the problem is with the male partner and for the remaining 27% there are problems in both partners. The cause of infertility is unknown

in about 15% of cases.<sup>2</sup>

Table 1 summarises the key steps that GPs may undertake with the couple. Although GPs may not be able to actively manage abnormalities identified in their assessments, the couple will feel reassured that things are progressing while they are waiting for a fertility clinic appointment. A summary flowchart is given on page 18.

## Supporting the couple

Once a couple starts trying to conceive, they typically do so with the expectation that they will soon succeed. It may be only after many months that they will visit their GP for advice, by which time

### IN SUMMARY

- GPs are often the first point of contact for an infertile couple. The GP's role includes taking a detailed history and examining both partners, supporting the couple (both medically and psychologically) through the entire process of investigation, arranging management and follow up, ordering fertility investigations, discussing treatment options and referring to specialists.
- The examination and investigation of the fertility of the male partner allows identification of conditions that commonly cause male infertility and that may be treated to restore natural fertility.
- GPs may refer the couple to specialists for treatment. Performing preliminary tests before referral will help to hasten the specialist investigations.
- Long-term follow up is important when a clinical or subclinical condition is identified in the male partner.

**Table 1. Key steps in managing a couple presenting with infertility**

- Provide ongoing support for the couple
- Take reproductive history – address readily reversible causes of conception difficulty (e.g. sexual timing)
- Perform physical examination and detailed medical history
- Investigate and manage reversible causes (e.g. sexual dysfunction)
- Order fertility investigations (e.g. semen analysis, endocrine tests)
- Discuss treatment options based on test results
- Refer to specialists for assisted reproductive technology treatments
- Follow up medical, psychosexual or emotional conditions associated with infertility

they will have experienced uncertainty, disappointment and anxiety about what might be wrong. The GP has an important role in supporting the couple through the process of investigation and management of infertility.<sup>3</sup>

Feelings of loss, grief and anxiety are common when people realise that they may not conceive naturally. Concerns are often associated with anxiety about fulfilling the desire for parenthood. Depression may relate to feelings of inadequacy and loss, such as failure to fulfil aspired parenting roles, unsuccessful fertility treatment and social comparison with other people who do have children. Moreover, fertility treatments can be physically and emotionally demanding and couples will require support and understanding.

The GP's role is vital, both from a medical and psychological perspective. Some people prefer to take their concerns to their GP, rather than burdening their family or friends. Some will benefit from practical assistance and others may seek emotional and psychological support. Approaches to supporting the couple include:

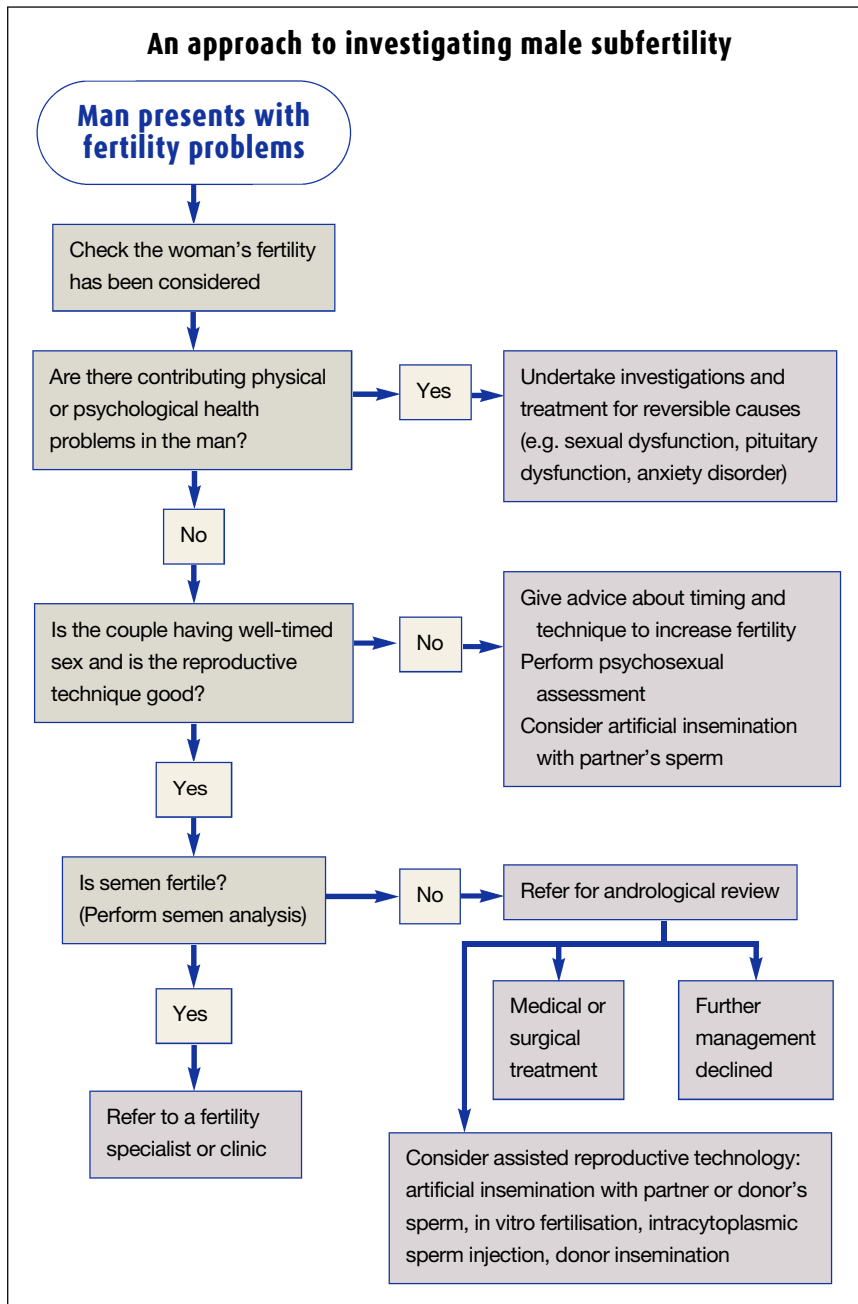
- acknowledging emotional responses to infertility and treatment, as well as the impact of these on the couple's day-to-day life
- acknowledging men's experience of infertility treatment (women are often the focus as they more frequently undergo major medical procedures)
- providing empathy and normalising feelings of grief and loss, and assisting the couple with managing their feelings when treatment is not available
- supporting the couple in communicating and working together
- referring the couple to a psychologist or counsellor if necessary.

## Male infertility



Women are often the focus of fertility investigations but the man should not be overlooked. There is much a GP can do to help a man with fertility problems, including medical examinations and investigations, referral and providing ongoing support to the couple.

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**Initial consultations**

It is best for the couple to be seen together at the initial consultation. If a couple is concerned enough to seek medical help, they should not be discouraged with comments such as ‘You should wait at least 12 months’. The later discovery of a fertility defect that would have been

apparent on initial screening will cause resentment.

Of couples discontinuing contraception, 90% conceive within 12 months; however, initial investigations can be organised as soon as a couple expresses concern, especially if the woman is over 35 years of age. Assessment should

commence with inexpensive, noninvasive investigations of the female partner’s ovulation cycle and the male partner’s fertility.<sup>1</sup>

Prepregnancy counselling is indicated, including advice to the woman about dietary supplements, lifestyle and immunisation. Smoking cessation is also important for men as apart from harming their health and exposing their partner to passive smoking, it may have detrimental effects on sperm DNA. Healthy weight management should be encouraged as there are some data associating obesity with both poorer semen quality and decreased testosterone levels.<sup>4,5</sup>

**Assessment of medical and reproductive history**

Preliminary questioning can help in understanding the couple’s situation. Information gained should include the couple’s ages, how long they have been trying to conceive, whether they have any idea why they have not been able to conceive and whether they have ever conceived previously, either together or separately. Discussion of this last topic may be sensitive with respect to any previous pregnancy terminations or relationships that may not have been disclosed to the other partner.

Male infertility is then evaluated via a general medical history and physical examination, focusing on the reproductive system, as described below.<sup>1,6</sup>

**Sexual intercourse: timing and technique**

It is vital that the couple is having regular and appropriately timed vaginal intercourse. Consider the time since contraception was stopped and the likely speed of its reversibility (e.g. oral contraceptive pill versus medroxyprogesterone acetate) to derive the true time of exposure to possible pregnancy. The man should be asked if he has experienced difficulty obtaining or maintaining erections that

**Table 2. Causes of male infertility<sup>1,7</sup>**

- Poor spermatogenesis – over 60% of cases
- Obstructive azoospermia – about 25% of cases
- Disorders of intercourse or ejaculation – about 10% of cases
- Sperm antibodies – about 5% of cases
- Hormonal deficiency due to pituitary/hypothalamic problems – rare (about 1% of cases)

are sufficient for completion of intercourse and whether he usually reaches orgasm and ejaculates during intercourse.

Record the frequency and timing of intercourse and ascertain whether the couple is aware of their fertile times (advice may be needed about the signs of this). Intercourse should take place at least every second day during the 'fertile phase', which can be predicted by the length of previous menstrual cycles. The luteal phase is usually about 14 days, so a woman with 26- to 32-day cycles would ovulate between days 10 and 17, this being the 'fertile week'. Women with less frequent cycles are probably not ovulating regularly and require further review.

A basal temperature chart is useful when assessing the current menstrual cycle, the likelihood and timing of ovulation and the appropriateness of coital timing. Although the chart does not help with the exact timing of intercourse, it indicates when intercourse can go back to being spontaneous, rather than advised by the time of the month.

### Fertility in the male partner

The assessment of the male partner allows the identification of conditions that may be treated in order to restore natural

fertility. It also allows the detection of health problems that are more common in infertile men as well as testing to inform the couple about their chances of natural fertility so they may decide about assisted reproductive technology (ART) choices.

The taking of the reproductive history of the male partner includes asking about:

- prior paternity
- pubertal development – poor progression suggests underlying reproductive issues
- history of undescended testes – a risk factor for infertility and testis cancer
- previous genital infections or trauma – risk for testis damage or obstructive azoospermia
- symptoms of androgen deficiency (see [http://www.andrologyaustralia.org/docs/clinical-summary-guide04\\_May2010.pdf](http://www.andrologyaustralia.org/docs/clinical-summary-guide04_May2010.pdf) for information on symptoms of androgen deficiency)
- previous genital surgery – undescended testes, testicular torsion, hernias, prostatic surgery, urinary catheterisation
- exposure to toxic agents – producing transient or permanent damage to spermatogenesis
- general health – diet, weight, exercise, smoking.

Table 2 shows the common causes of male infertility.<sup>1,7</sup> Poor spermatogenesis accounts for over 60% of cases of male infertility, most of which are unexplained and usually described as 'idiopathic' infertility, although genetic explanations are now more often being provided. Spermatogenic failure can also be due to many different insults (such as radiotherapy, chemotherapy, orchitis, vascular damage, excessive heating) and is associated with undescended testes. Semen quality is variably impaired and includes the absence of sperm (azoospermia) or reduced sperm number (oligospermia), often with defective motility (asthenospermia) and/or morphology (teratospermia). Some men

have profound reductions in all three parameters and others may only have a single defect.

Obstructive azoospermia accounts for about 25% of cases of male infertility. Previous vasectomy is a leading cause, but other common disorders include congenital absence of the vas (impalpable vasa and low volume, acidic semen resulting from absent seminal vesicles), epididymal scarring following sexually transmitted diseases, and ejaculatory duct obstruction from prostatic cysts, infection, urinary catheterisation or surgery.

Disorders of intercourse or ejaculation account for about 10% of cases of male infertility. This heterogeneous group includes erectile dysfunction from any cause as well as retrograde ejaculation or 'functional' defects in sperm transport resulting from, for example, diabetic neuropathy, retroperitoneal lymph node dissection or spinal cord injury. Intercourse may occur too infrequently or at the wrong time of the cycle. Psychosexual problems are also common.

Sperm antibodies account for about 5% of cases of male infertility. Antibodies that bind sperm may impede their motility, survival or ability to attach to the egg and can occur after obstruction (e.g. vasectomy) or testicular trauma. Sperm antibodies are often of unexplained causation.

Hormonal deficiencies due to pituitary or hypothalamic problems are rare (about 1% of cases), but detection is essential as specific treatment is available (e.g. gonadotropin replacement therapy or cabergoline for prolactinoma) and is very effective in restoring both fertility and testosterone secretion. Androgen abuse is not uncommon in younger men and reversibly suppresses follicle stimulating hormone (FSH), luteinising hormone (LH) and spermatogenesis.

### Physical examination

The examination of the male partner of an infertile couple includes a general

review, but should focus on the reproductive system. It should include the following:<sup>1,6</sup>

- general examination – i.e. acute or chronic illness, nutritional status
- the degree of virilisation – poor virilisation suggests androgen deficiency
- genital examination
  - examining the testes: small and/or soft testes suggest spermatogenic failure and testicular volume under 4 mL suggests Klinefelter's syndrome
  - the presence of vas deferens: these may be congenitally absent
  - epididymides examination: thickening or cysts may suggest previous infection and resultant obstructive problems
  - examining for varicoceles: detected when standing, coughing or performing Valsalva manoeuvre
  - examining the penis: abnormalities such as Peyronie's disease may interfere with sexual intercourse
- examining the prostate – if history suggests prostatitis or sexually transmitted infections; older infertile men are more at risk of incidental prostate disease.

### Common problems seen in infertile men

GPs should be alert to the most common problems associated with infertility in men (Table 3). Testis cancer is more common in men with idiopathic infertility, especially in those with a history of undescended testes (cryptorchidism) and particularly if bilateral. The risk persists but is reduced after surgical correction. Careful examination and ultrasonography is indicated, as well as education about self-examination.

Androgen deficiency (hypoandrogenism) is also more common in infertile men, especially those with testicular atrophy. Its identification and treatment greatly improves quality of life and

prevents long-term problems such as osteoporosis. Klinefelter's syndrome (prevalence 1:650 men) is frequently undiagnosed and should be considered when men present with infertility and azoospermia. Androgen replacement should be delayed until fertility issues are resolved.

Psychosexual and relationship difficulties are common following the recognition of male infertility. Men may experience feelings of guilt, loss of masculinity or erectile problems.

Severe system illnesses, such as chronic renal or liver disease, or chronic opiate usage for analgesia, may lead to poor spermatogenesis and/or androgen deficiency.

### Fertility investigations Semen analysis

Analysis of semen is the most important investigation for male infertility and several points must be emphasised.<sup>8,9</sup> Men should abstain from sexual activity for two to seven days before the sample is collected.<sup>8</sup> The ejaculate is best collected at a specialised laboratory but may be done at home if care is taken to avoid temperature fluctuation and if transport to the laboratory is rapid (ideally within one hour).<sup>8</sup> If ejaculation by masturbation is difficult, collection may be obtained by interrupted intercourse. Condom collection devices are available from specialised laboratories; ordinary condoms cannot be used because they contain agents that interfere with sperm motility.

It is recommended that two semen analyses are done, approximately six weeks apart. The second test should be performed in a specialised fertility laboratory if an initial test result is poor. The laboratories used should comply with WHO guidelines for semen analysis,<sup>8</sup> as do those associated with fertility units.

Semen analysis following WHO guidelines helps estimate the chance of

### Table 3. Common problems seen in infertile men

- Testis cancer – more common in men with idiopathic infertility
- Androgen deficiency (hypoandrogenism) – more common in infertile men, particularly in those with testicular atrophy
- Psychosexual and relationship difficulties – common following the recognition of male infertility
- Severe system illness (e.g. chronic renal or liver disease) or chronic opiate usage for analgesia – may lead to poor spermatogenesis and/or androgen deficiency

natural pregnancy. The total number of motile sperm, the pattern of motility and the proportion of sperm with normal morphology correlate with in vivo pregnancy rates. Data from the analysis are then interpreted, based on epidemiological data and observational data from ART treatments to estimate fertility prospects. Semen analysis is not a direct test of sperm function. In some patients with idiopathic infertility (by definition having a normal semen analysis), a profound defect in sperm function may become apparent when observing sperm and egg interaction during in vitro fertilisation (IVF).

The WHO reference intervals have recently been revised based on the 5th percentile values of healthy men whose partners conceived within 12 months of stopping contraception (Table 4).<sup>8</sup> Some laboratories may still be using the old (1999) guidelines but it is anticipated that the new guidelines will gradually be adopted throughout Australia. The updated reference intervals are not absolute indicators of fertility; for example, although 15 million sperm/mL is the agreed lower value for sperm density,

this does not mean that men with a sperm count of 4 million sperm/mL are sterile. About 30% of such couples will have a spontaneous pregnancy over a two- to three-year period. Major determinants of future pregnancy success are the severity of the semen defects, the length of time the couple have been trying to conceive and the age and fertility of the female partner.

### Endocrine tests

When semen quality is poor or there are other features of reproductive problems (e.g. small testes, androgen deficiency) then the tests below can be performed.

#### Serum FSH levels

Serum FSH levels are elevated when spermatogenesis is poor (primary testicular failure). The upper reference value for FSH in normal men is 8 IU/L; however, some laboratories quote a misleadingly high upper limit due to the assay manufacturer's inclusion of older men and those with unrecognised fertility problems in the reference population. When investigating an azoospermic man, an FSH level of 14 IU/L strongly suggests spermatogenic failure whereas a level of 5 IU/L raises the question of obstructive azoospermia.

The FSH level is not always reliable and testis biopsy may be needed to investigate azoospermia.

#### Serum testosterone

The serum testosterone level is often normal in men with infertility, even in men with spermatogenic problems. In some men with more severe testicular problems, testosterone levels fall and a reciprocal rise in serum LH levels is seen. This indicates androgen deficiency and requires evaluation. Rarely, pituitary problems result in low serum FSH, LH and testosterone levels (secondary testicular failure). A rise in prolactin level suggests a prolactinoma.

**Table 4. WHO normal ranges for semen analysis<sup>3\*</sup>**

| Semen characteristic | WHO normal range                                    |
|----------------------|---|
| Volume               | 1.5 mL or more                                      |
| pH                   | 7.2 or higher (i.e. more alkaline)                  |
| Sperm concentration  | 15 million or more sperm/mL                         |
| Motility             | 40% or more motile within 60 minutes of ejaculation |
| Normal morphology    | 4% or more  |
| Vitality             | 58% or more live                                    |
| White blood cells    | Fewer than 1 million/mL                             |
| Sperm antibodies     | Less than 50% motile spermatozoa with binding       |

\*Based on 5th percentile of values from a group of recent fathers whose partners became pregnant within 12 months of stopping contraception.<sup>3</sup>

### Ultrasound

Testicular ultrasound scanning should be considered if the man has a past history of undescended testes or testicular atrophy, or any abnormality of the testes on examination.

### Tests performed by specialists

Imaging investigations for obstructive azoospermia (e.g. bladder base structures) are best performed by urologists. Testis biopsy is occasionally needed to establish whether azoospermia is due to spermatogenic failure or obstruction, especially when the FSH level is normal borderline. This can be performed by needle biopsy under local anaesthetic or by open biopsy.

Severe spermatogenic failure is associated with karyotypic abnormalities and deletions of the Y chromosome and these have implications for the health of offspring. Fertility specialists usually order these tests. However, if Klinefelter's syndrome is suspected (e.g. testis volume is less than 4 mL) the GP should order a karyotype analysis.

### Treatments for male infertility

GPs may advise couples how to maximise fertility and explain to them the reversible causes of conception difficulties. Many

patients should be referred to specialists, particularly if ART or donor insemination is likely to be required.<sup>1</sup>

### Protecting and preserving fertility

Strategies to protect fertility are wide-ranging. They include vaccination for mumps, sperm cryopreservation (prior to chemotherapy, vasectomy or androgen replacement), safe-sex practices to avoid sexually transmitted infection damage or obstruction, and early surgical correction of cryptorchidism.

### Improving natural fertility

Specific medical treatments to improve natural fertility exist for a minority of infertile men. Individuals suffering from the conditions below may benefit from specialised management:

- pituitary hormonal deficiencies – gonadotrophin treatment
- hyperprolactinaemia – dopaminergic drugs
- genitourinary infections – antibiotics if active infection present
- erectile and psychosexual problems – erectile dysfunction therapies, counselling
- men who require withdrawal or substitution of drugs – opiates, sulfasalazine, anabolic steroids.

Varicoceles are more common in infertile men, but the evidence that intervention improves fertility is limited. A recent Cochrane review did not provide support for intervention.<sup>10</sup>

### **Improving sexual intercourse timing and technique**

If the couple are not having well-timed sex or are not using appropriate techniques, medical advice could include information about cycle length, mucus signs and the use of a temperature chart. In circumstances where repeated intercourse is difficult, the use of a urinary LH kit may be recommended. Behavioural problems such as an inability to maintain an erection and/or inability to ejaculate during vaginal sex require psychosexual assessment and counselling. If there are organic causes for erectile dysfunction (such as vascular disease or diabetes), treatment might include drugs such as phosphodiesterase type 5 (PDE5) inhibitors. If these interventions fail, artificial insemination using the man's semen can be considered.

### **Assisted reproductive technology**

ART procedures play a major role in fertility treatment and account for over 3% of births in Australia. ART options range from artificial insemination with the male partner's sperm to conventional IVF (where there are thousands of motile sperm in a dish with mature oocytes) through to intracytoplasmic sperm injection (ICSI) of single sperm into the oocyte (if the man has severe spermatogenic problems).

#### **Intracytoplasmic sperm injection**

ICSI is possible even if only a few viable sperm are present in the semen or from testis biopsy. Men with severe spermatogenic problems (primary or secondary) and their partners now enjoy similar pregnancy prospects to couples with other types of infertility. Obstructive azoospermia is increasingly being

managed with ICSI, using sperm recovered from the epididymis or testis through needle biopsy under local anaesthesia.

The largest group of couples requiring ART is those with vasectomy-related infertility. For selected couples it is a cost-effective approach, especially if the vasectomy was performed years ago and

the woman is older and/or of unproven fertility.

ICSI may also be used in other settings, including ejaculatory duct obstruction that cannot be surgically remediated, as an alternative to electro-ejaculation (e.g. in patients with diabetes or spinal cord injury) or when sperm antibodies are present. IVF/ICSI is now a very real

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solution for many couples when there is male subfertility, but it does place a burden on the couple, particularly the female partner.

In the early days of IVF there was a low chance of success but today's results are far more encouraging. The critical factor is the age of the woman. As for natural pregnancies, the success rate

should not be thought of as 'chance per attempt', but rather 'chance of conception after a number of attempts'. An analysis of 6164 patients undergoing 14,248 cycles in Boston, USA, reported the cumulative live-birth rate after six cycles was 72%.<sup>11</sup> Among patients who were younger than 35 years of age, the corresponding rate after six cycles was

86% and for those 40 years of age or older, 42%.

#### Donor insemination

The advent of ICSI, permitting fatherhood when only a few sperm are present, has resulted in reduced use of donor insemination, although the latter is an option for men with complete sperm production failure. The sperm donor may be chosen by the couple or the sperm may be obtained anonymously from a sperm bank. In several states, legislation requires the recording of the details of the donor, the recipient couple and the baby, so that donor-conceived individuals can choose, when they reach adulthood, to contact their biological father.

#### Specialist referral

GPs should not delay referral after the initial tests (semen analysis for the male partner and mid-luteal hormones for the female partner as well as confirmation of her rubella and varicella immunity) have been arranged.

Men with fertility problems are commonly referred to specialists, including endocrinologists, urologists, fertility specialists, ART clinics, psychologists and approved counsellors. Regional lists of ART clinics accredited by the Reproductive Technology Accreditation Committee are available from the Fertility Society of Australia (<http://www.fertilitysociety.com.au/patients-information>).

#### Follow up of conditions associated with infertility

Some infertile men require long-term management, including periodic observation for late-onset androgen deficiency, testicular cancer and specific health issues, such as those pertaining to Klinefelter's syndrome or pituitary deficiency.

Long-term surveillance by the GP to identify progression to clinical androgen deficiency in men who have evidence of



**Consultant's comment**

It is not uncommon for the male partner in an infertile couple to be the sole cause of the problem. The man has often been overlooked in the past, mainly because of the excellent achievements made with IVF.

A urologist or andrologist should be involved in the evaluation and treatment of the infertile couple, especially in cases of obstructive azoospermia. Microsurgery can restore sperm in nearly all men who have had a vasectomy and vasoepididymostomy can alleviate epididymal obstruction. Ejaculatory duct obstruction can be cured endoscopically in many cases, immediately restoring fertility. Cure of varicoceles has always been controversial, but sperm can return to the ejaculate in cases of nonobstructive azoospermia after high ligation, again through the use of the operating microscope.<sup>1,2</sup>

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borderline androgen deficiency (e.g. normal serum testosterone, a mildly elevated serum LH but no clinical evidence of deficiency) requires regular assessment of symptoms and blood samples every one to three years initially and then, if the results are stable, every five years. Monitoring should also include evaluation of the couple's psychological or emotional state and appropriate referral if required.

**Conclusion**

GPs play a vital role when couples have difficulty conceiving. They are often the first point of contact for a couple when infertility is suspected and they may be involved with the couple through the entire process of fertility investigations and treatment. Male infertility can sometimes be overlooked, as women are often the focus of fertility investigations. However, as outlined in this article, there is much a GP can do to help a man with fertility problems, including performing medical examinations, organising investigations and referrals and providing ongoing support to the man and his partner.

Further information on male infertility and other topics covered in this article is available on the Andrology Australia website (<http://www.andrologyaustralia.org>) under 'Clinical summary guidelines'.

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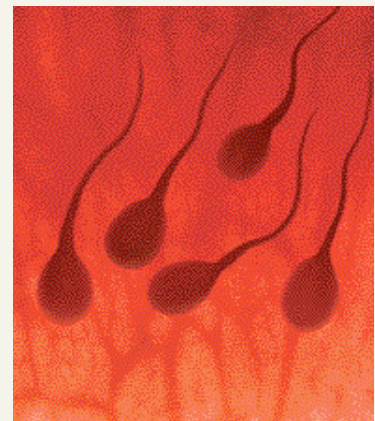
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**COMPETING INTERESTS:** Professor McLachlan has received funding for investigator-initiated studies from Mayne Pharma Pty Ltd and Bayer Schering Pharma Ltd and acted as a consultant for Acrux Ltd, Mayne Pharma Pty Ltd and Bayer Australia Ltd.

Professor Kovacs has received honoraria for lectures from MSD-Schering Plough/Organon.  
Associate Professor Cook: None.

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