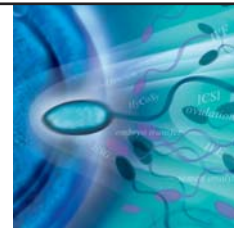# Management of the infertile couple

BACKGROUND With the further development of reproductive technology over the past 2 decades, options for subfertile couples have greatly increased.

OBJECTIVE This article discusses the assessment of common male and female causes of infertility and describes a logical routine for the investigation and treatment of the subfertile couple using a flow chart approach.

DISCUSSION We suggest an approach to assessment for general practitioners, and outline the likely course of more sophisticated testing and treatments that their patients may then experience.

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The first point of contact for a couple having difficulty conceiving is usually their family doctor. In order to help general practitioners understand and organise a systematic approach to infertility, we have developed a 'flowchart' approach to the subfertile couple (*Figure 1*).

If a couple are concerned enough to seek medical help, they should not be ignored with comments such as, 'you should wait at least 12 months'. While it is true that of couples discontinuing contraception, 90% conceive within 12 months, there is no reason to recommend delaying investigations. We believe that initial investigations can be organised as soon as a couple express concern, especially if the woman is of advancing age. Therefore, it is our routine to commence with cheap and noninvasive investigations of female ovulation and male fertility.

Whenever possible, the couple should be seen together. It is recommended that pre-pregnancy counselling be undertaken at the first consultation including advice about diet, exercise, alcohol intake and smoking cessation, and screening for immunity to both rubella and varicella. In line with National Health and Medical Research Council recommendations, folate supplementation should be commenced to decrease the risk of neural tube defects.

Are the couple having well timed sex/technique?

As the first requirement for conception is the entry of an adequate number of spermatozoa into the cervical canal at the appropriate time, it is vital to ensure that the couple are having effective intercourse. The family doctor is ideally placed to ascertain this. As the frequency and timing of intercourse is difficult to assess retrospectively and ovulation impossible to cal-
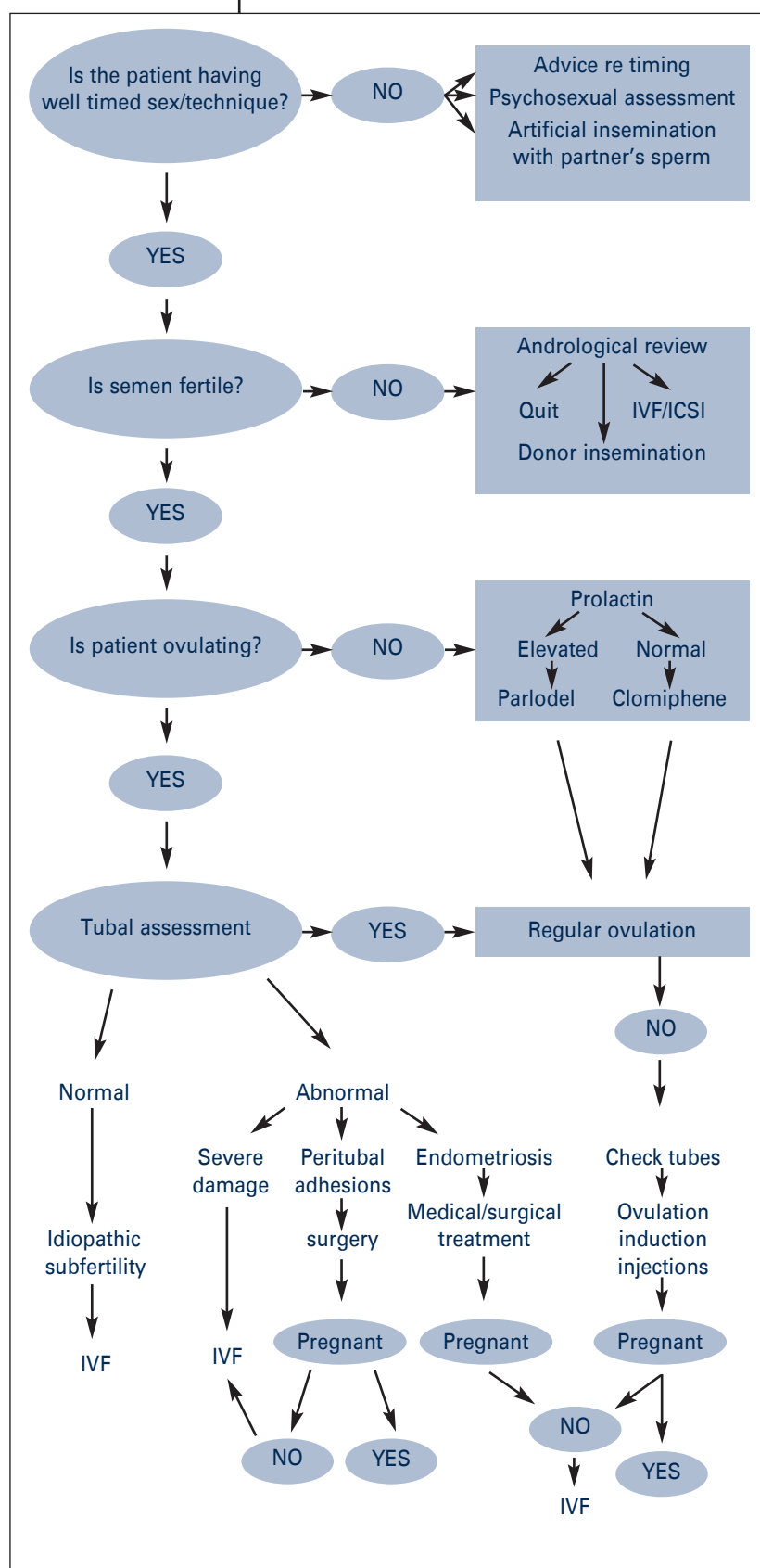
Figure 1. Subfertility flowchart

culate, we have developed a series of questions to determine the adequacy of coitus. The first question to ask, directed toward the man, is: 'Any difficulty with erections and being able to maintain these to have adequate intercourse on demand?' The next question directed toward the woman, is: 'Do you have any difficulty with penetration such as pain or discomfort?' We then ask the male partner whether he, 'usually reaches orgasm, and ejaculates during intercourse'? Finally, there is discussion about the amount of semen that is lost after intercourse. It is reported as usual for a woman to use a tissue to collect semen spill. Women have to be reassured that adequate quantities of semen will reach the cervix despite vaginal backflow. This can be done with a postcoital microscopic examination of the cervical mucus after intercourse. The presence of sperm in the mucus confirms coital adequacy.

With respect to the timing of intercourse, our usual advice is that intercourse can take place at any time during the menstrual cycle, but at least every second day during the 'fertile phase'. The fertile phase can be predicted by assessing the length of previous menstrual cycles. We know the luteal phase is fairly constant at about 14 days, so a woman with 26–32 day cycles would usually ovulate between days 10 to 17, this being the 'fertile week'. Women who have less frequent cycles are probably not ovulating regularly and may benefit from ovulation induction with clomiphene citrate.

A basal temperature chart (BTC) is very useful in assessing the current menstrual cycle, time of ovulation and the appropriateness of coital timing. Although this does not help with the exact timing of intercourse, it will indicate when intercourse can resume being recreational rather than procreational. The BTC allows a retrospective assessment of coital timing. Instructions for recording a temperature chart (including coital timing) are shown in *Patient education* page 139 this issue.

Is the male partner fertile?

The male partner should always be evaluated as part of the 'couple focussed' approach in modern fertility practice. This allows identification of conditions that are treatable to restore natural fertility, the detection of health problems that are more common in infertile men, and the performance of tests that inform the couple about their chances of natural fertility and their decisions about assisted reproductive technology (ART) choices.

Andrological evaluation

The history of the male partner's reproductive status includes assessment of pubertal development, any history of undescended testes (cryptorchidism) or genitourinary infection, and symptoms of testosterone deficiency. Examination should focus on the degree of virilisation and genital examination (especially testis size/consistency, vasa and epididymides, varicocele). Varicoceles are more common in infertile men, but their relevance to infertility remains unclear and proof that fertility prospects are improved by their removal is lacking.

Causes of male infertility

The most common causes of male infertility are:

- poor spermatogenesis – which accounts for over 60% of cases, the majority being unexplained or 'idiopathic'; increasingly genetic explanations are being provided. Semen quality is variably impaired with no sperm (azoospermia), or reduced sperm number (oligospermia) often with defective motility (asthenospermia) and/or morphology (teratospermia). The function of individual sperm is often reduced
- obstruction azoospermia – this accounts for about 25% of cases. Prior 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 postsexually transmitted infections, or ejaculatory duct obstruction from prostatic cysts, infection, urinary catheterisation or surgery
- disorders of intercourse or ejaculation – these account for about 10% of cases. This heterogeneous group includes erectile dysfunction of any cause, and retrograde ejaculation or 'functional' defects in transport resulting from diabetic neuropathy, retroperitoneal lymph node dissection or spinal cord injury. Also, intercourse may occur too infrequently or at the wrong time of the cycle
- sperm antibodies – these account for about 5% of cases. Antibodies that bind sperm may impede their motility, survival or ability to attach to the egg and can follow obstruction (eg. vasectomy), or testicular trauma but are often of unexplained causation
- hormonal deficiency due to pituitary/hypothalamic problems is rare (1%), but its detection is essential as specific treatment is available (eg. gonadotropins, cabergoline) that restore 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.

Infertile men – common problems

A history of undescended testes (cryptorchidism) increases the risk of testicular cancer, particularly if bilateral. This risk persists despite surgical correction. Careful palpation and ultrasonography is indicated along with education about self examination. Testosterone deficiency (hypoandrogenism) is also more common in infertile men, especially those with testicular atrophy, and its identification and treatment greatly improves quality of life and prevents long term problems such as osteoporosis. Klinefelter syndrome (incidence 1:600 men) frequently escapes diagnosis, but an opportunity for diagnosis arises when these men present with infertility and azoospermia. Psychosexual difficulties are common following the recognition of male infertility with feelings of guilt, loss of masculinity, or erectile and relationship problems.

Investigations

Semen analysis

This is the key investigation for male infertility. Several points must be made:

- the quality of the analysis depends upon the laboratory – many private laboratories do not use World Health Organisation guidelines and do not produce useful motility and morphology results. It is recommended that two semen analyses be performed 4–6 weeks apart. In men whose initial test is poor, the second test should be performed in a specialised laboratory (these are often associated with ART programs)
- semen analysis helps estimate the chance of natural pregnancy; the total number of motile sperm, the pattern of motility, and the shape correlate with in vivo pregnancy rates. Semen analysis is not a direct test of the ability of sperm to seek out, bind and fertilise an egg; these latter abilities may be deficient in some men with apparently normal semen quality. Such couples account for a proportion of 'idiopathic' infertility.

Endocrine tests

Elevated FSH levels are seen when the testis (and spermatogenesis) has been damaged (primary testicular failure). Serum testosterone is often normal but in some men with more severe testicular problems,

levels fall and a reciprocal rise in serum LH is seen. Rarely pituitary problems result in low serum FSH, LH, and testosterone levels (secondary testicular failure); a rise in prolactin suggests a prolactinoma.

Specialised tests

Specialised tests include:
- testis biopsy – occasionally needed to be certain whether azoospermia is due to spermatogenic failure or obstruction
- genetic tests – severe spermatogenic failure is associated with higher rates of karyotypic abnormality and with deletions of the Y chromosome; both have implications for the health of offspring.

Treatments for male infertility

Strategies to protect/preserve fertility are wide ranging and include mumps vaccination, sperm cryopreservation (prechemotherapy, vasectomy), safe sex practices, and early surgical correction of cryptorchidism.

Specific medical treatments to improve natural fertility exist for a minority of infertile men including those with pituitary hormonal deficiency or hyperprolactinemia, genitourinary infection, erectile and psychosexual problems, and through the withdrawal of drugs (opiates, salazopyrine, anabolic steroids).

Intracytoplasmic sperm injection

In vitro fertilisation (IVF) procedures now play a major role in infertility, but obviously place a heavy burden on the female partner. Intracytoplasmic sperm injection (ICSI) for men with severe spermatogenic problems has made a huge impact – if a few viable sperm are present in the semen or in testis biopsy material, they are capable of initiating normal pregnancies. Obstructive azoospermia is increasingly managed with ICSI using sperm recovered from the epididymis or testis under local anaesthesia. The largest single group is vasectomy related infertility. Surgical vasectomy reversal offers only a 50% prospect of fertility in selected cases (vasectomy <10 years ago and with a younger female partner of established fertility).

In addition, ICSI is used in other settings including ejaculatory duct obstruction, as an alternative to electro-ejaculation (diabetes, spinal cord injury), and when there are sperm antibodies present.

Donor insemination

The advent of ICSI, permitting fatherhood when only a few sperm are present, has resulted in a reduction in the use of donor insemination, but the latter remains an option for men with complete failure of sperm production.

Artificial insemination

Artificial insemination has a place where mechanical problems are present, but its value when male subfertility exists is less convincing.

Is the female partner fertile?

Initial assessment of the female partner focusses on the evaluation of ovulation and tubal patency.

Is the woman ovulating?

Fertility is no different from other areas of medicine, and the routine of 'history, examination and special tests' is used for assessing ovulation. A history of regular, painful menstrual cycles associated with premenstrual symptoms, mid cycle pain (Mittelschmerz) and mid cycle spotting is indicative of regular ovulation. However, menstruation can occur without ovulation, as the production of oestrogen may be sufficient to induce proliferation of the endometrium, and the later withdrawal of oestrogen can result in menstruation without requiring the presence of progesterone.

Other important symptoms of ovarian activity are the classic changes in the cervical mucus that have been widely publicised as part of the 'Billings method' of fertility control. The quantity and quality of cervical mucus act as a 'bio-assay' of oestrogen and progesterone secretion. These steroid hormones affect the water and sodium chloride concentration within the cervical mucus and result in biophysical characteristics.

Classically there are 'dry days' after menstruation with little mucus, and then the quantity of mucus gradually builds up as oestrogen is being secreted by the developing follicle. When there is maximal unopposed oestrogen secretion, the mucus is copious, clear, and stretchy-like egg white (the fertile pattern). As soon as ovulation occurs and progesterone is secreted, the quality of the mucus changes to become viscid, opaque and nonstretchy (the infertile pattern). Many women can discern these changes and use the presence of fertile mucus to help with the timing of intercourse.

With respect to examination, the temperature chart is also a good bioassay of the menstrual cycle. The thermogenic effect of progesterone results in the char-

acteristic postovulatory rise of temperature. By documenting days of coitus, appropriate timing can be assessed retrospectively.

The midluteal (approximately day 21) serum progesterone is most commonly used to document ovulation. This should be combined with a serum prolactin as elevated levels may cause subfertility and inhibit ovulation. Serial ultrasound examinations can document follicular development and ovulation, but are expensive and time consuming and have little place in ovulation detection. Similarly, while serial LH measurements are useful in pinpointing the time of ovulation, they are not helpful in determining that ovulation has taken place. In women with amenorrhoea, the measurement of FSH levels can diagnose premature menopause if it is elevated, and a raised LH/FSH may suggest polycystic ovarian syndrome.

Tubal function

Once it has been shown that the man is relatively fertile and that ovulation is occurring, or has been induced with three successful ovulations in anovulatory patients, a test of tubal function should be undertaken. This usually consists of a laparoscopy with hydrotubation in association with hysteroscopy and curettage. This not only confirms tubal patency but allows assessment of tubal normality, the presence of fimbria, and the degree of tortuosity. Other pathology such as endometriosis or adhesive disease may be addressed at the same time.

Treatment for female infertility

Is the woman having well timed sex/technique?

If the answer is 'no' then the following remedial options are possible. Appropriate timing advice about using cycle length and mucus symptoms may be assisted with a temperature chart. In circumstances where repeated intercourse is difficult, the use of an ovulation kit based on measuring urinary LH may be recommended. If there is a 'technical' problem with penetration, psychosexual assessment and counselling may be considered. If that fails, artificial insemination using the partner's semen can be performed.

Ovulation induction

If the woman is not ovulating, or is doing so irregularly, ovulation induction should be undertaken. It is essential that the male partner's semen analysis be checked before embarking on ovulation induction. The first step is

to exclude a raised prolactin. If this is elevated four times above the upper limit of normal, specialised investigation of pituitary fossa by magnetic resonance imaging is indicated (MRI has replaced CT – at least among endocrinologists – as it is more precise). Elevated levels of prolactin can be treated by bromocryptine or cabergoline. Raised levels of prolactin may result in a short luteal phase and subsequent subfertility.

The first line of treatment is clomiphene citrate administered as a 50 mg tablet for 5 days (usually day 5–9 of the cycle). In the case of polycystic ovary syndrome with irregular cycles, a starting dose of 25 mg per day is appropriate. The dose can be increased each cycle by 50 mg to a maximum dose of 150 mg (three tablets per day). The response is usually assessed by using a temperature chart including coital charting and midluteal assessment of oestradiol and progesterone levels. Should clomiphene citrate induction be unsuccessful, one needs to resort to ovulation induction using gonadotrophins. This is complicated and time consuming, and necessitates careful monitoring by experts in reproductive endocrinology. Even in expert hands, multiple pregnancy rates of 20% are reported.[1]

In women with anovulation as the only cause of subfertility, outcome is often successful within three ovulations. If a conception does not occur, further investigations are needed.

Tubal assessment

If tubal assessment shows a normal pelvis, a diagnosis of idiopathic infertility is made. The only treatment is IVF. If laparoscopy reveals severe tubal damage, again IVF is the treatment of choice. If the tubes are relatively normal, but peritubal adhesions are detected, laparoscopic salpingolysis is indicated. If endometriosis is detected, medical or surgical treatment is indicated. If pregnancy does not occur despite these measures, IVF is the last resort.

IVF

The endpoint for all therapeutic pathways is IVF. The IVF process can be divided into six steps:
- controlled ovarian hyperstimulation. This is achieved by the use of FSH injections combined with a GnRH analogue to prevent spontaneous ovulation
- monitoring is undertaken by oestrogen measurement and/or ultrasound assessment of follicular growth
- the oocytes are recovered transvaginally under ultra-

sound control, usually under intravenous sedation or general anaesthesia

• IVF with or without ICSI is undertaken. Embryos are cultured in vitro for 2–6 days
• embryo transfer (either one or two) is undertaken
• excess embryos of good quality are frozen and cryo-genically stored.

The likelihood of a successful pregnancy depends on the woman's age and fertility status. Male factors have little effect on the success rate providing live sperm can be obtained from anywhere in the reproductive tract – as ICSI allows fertilisation and embryo generation in the majority of male factor infertility. Generally, success rates of 30–40% per fresh and 15–20% per frozen cycle can be expected. With repeated cycles, the chance of pregnancy compounds, and women under 35 years of age have a greater than 60% chance of conceiving within two stimulated cycles and associated frozen embryo transfers.

Approximate costs

Costs differ from unit to unit, the type of IVF, and the patient's insurance status. In Australia, with Medicare and the 'safety net', IVF is highly affordable.

Conflict of interest: none declared.

Reference

1.   Kovacs GT, Pepperell RJ, Evans JH. Induction of ovulation with human pituitary gonadotrophin: the Australian experience. Aust NZ J Obstet Gynaecol 1989;29:315–8.

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ERRATUM

In the January/February issue of *AFP*, the article 'Yarning for better health' – Improving the health of an Aboriginal and Torres Strait Islander population, p 27–9, omitted Patrice Harald as one of the authors. *AFP* apologises to Ms Harald for this omission. An updated version of the article is available at: www.racgp.org.au/publications/afp_online.asp