PEER REVIEWED FEATURE POINTS: 2 CPD/2 PDP

The role of the GP in managing female infertility

Key points

- Preconceptual advice for females includes lifestyle advice, such as maintaining a normal body mass index, and a discussion on the detrimental effect of female age on fertility.
- A preconception blood screen should be performed in all women who want to conceive. This includes a full blood count, blood group, thyroid function tests, rubella, varicella, hepatitis B and C, and HIV serology.
- The next steps in management involve hormone assessment as well as a transvaginal ultrasound and assessment of the fallopian tubes using a hysterosalpingogram (HSG) or hysterosalpingo-contrastsonography (HyCoSy).
- Couples should be tested and referred after 12 months of trying to conceive if the female is younger than 35 years of age, and after six months if the female is older than 35 years.

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GPs often provide the first medical consultation for an infertile couple and can provide basic advice and education regarding fertility and conception. They can also determine which couples require referral to a specialist and the timing of this.

nfertility affects one in six couples in Australia1 and is an important part of clinical practice. A couple is regarded as having a fertility problem when they have not conceived after 12 months of regular unprotected sexual intercourse. Thorough and early evaluation of the infertile female is crucial in maximising her chances of conceiving spontaneously or with assisted reproductive technologies. GPs are in an important position to help achieve this by giving lifestyle advice, detecting patients who may need referral to a reproductive medicine specialist and ordering relevant tests to help the specialist treat the patient and her partner as efficiently and compassionately as possible.

Female infertility accounts for 40% of infertile couples, with male infertility having an equal frequency. The remaining 20% of couples have a joint problem or the cause of infertility is idiopathic.² This article focuses on female infertility but evaluation of both partners should commence at the same time.

An article entitled 'The role of the GP in managing male infertility' was published in the October 2010 issue of *Medicine Today*.³

ADVICE TO THE FEMALE PATIENT Female age

Age is the biggest factor in a woman's ability to conceive both spontaneously and with assisted reproductive techniques. Women are delaying childbearing and given that age is the biggest potential reproductive hurdle, GPs can help minimise this hurdle by simply reminding patients (and their partners) of this fact.

How and when can one sensitively mention age and its impact on reproduction? The opportunity to mention fertility issues could arise when female patients present to GPs for pap smears or a breast check. GPs with

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their continuity of care and patient rapport are in an ideal position to raise this potentially sensitive issue.

The decline in female fertility is directly related to the fact that women are born with all their oocytes and, as age increases, the proportion of oocytes remaining with genetic and metabolic errors that preclude a successful pregnancy steadily increases. There is a precipitous decline in oocyte function from the late 30s onwards.

Lifestyle factors

Modifiable lifestyle factors that may impact on a couple's time to conception and live birth outcome exist.⁴ Basic lifestyle advice, including a well-balanced diet and moderate levels of exercise should be a key starting point when advising a couple who would like to achieve a pregnancy.

Folate deficiency not only increases the risk of neural tube defects but it is also linked to infertility and an increased risk of spontaneous abortion.⁵ Hence, a daily intake of 0.4 mg folate (vitamin B_6) two months prior to conception and during the first three months of pregnancy is essential. (This dose should be 5 mg in women with a personal or family history of neural tube defects, in women with diabetes, and in women who are taking anti-epileptic medications.)

Adequate maternal levels of iodine are essential for fetal neurological development and if lacking can lead to intellectual impairment and cretinism. Many women in Australia have inadequate iodine intake⁶ and if attempting to conceive should take an oral daily 250 µg iodine supplement, in addition to a folate supplement.

Women who smoke cigarettes (and those exposed to passive smoke) are less likely to conceive and more likely to miscarry or have an ectopic pregnancy.⁷ Additionally, regular users of marijuana are at greater risk of infertility compared with nonusers.⁸

The exact level of alcohol intake required to affect fertility is unclear. The latest recommendation is that if a woman is trying to conceive, she should avoid alcohol altogether.⁴

There is sparse evidence regarding caffeine



intake and its effects on fertility. It is recommended that women trying to conceive or who are pregnant do not consume more than two cups of coffee per day.⁴

Extremes of body mass index

Overweight women

The prevalence of overweight and/or obese women in Australia is 52%, having more than doubled in the past 20 years.9 Although many people realise that being overweight or obese puts them at risk of cardiovascular disease and diabetes, few women realise the impact that excessive body fat has on their ability to fall pregnant. Obesity is associated with a significant disturbance in hormones that can affect the reproductive system. This is the case not only in overweight females but also in overweight males. Male obesity is associated with an increased incidence of low sperm concentration and sperm motility¹⁰ and it is therefore important to encourage weight loss in both partners if they are obese.

Obese women are almost three times as

OBESITY AND RELATED OBSTETRIC COMPLICATIONS/ ISSUES¹⁴

Antepartum

- Miscarriage
- Congenital abnormalities (e.g. neural tube defects and congenital heart disease)
- Difficulties visualising the embryo and fetus on ultrasound (hence a greater chance of missing the abnormalities listed above)
- · Large for gestational age/macrosomia
- Pre-eclampsia, gestational diabetes, deep vein thrombosis, pulmonary embolism, backache, urinary tract and wound infections
- Need for induction of labour

Intrapartum

- Difficulties with fetal monitoring and maternal analgesia (due to difficulties with access to epidural space and airway)
- Prolonged and obstructed labour
- Birth trauma for both mother and baby
- Caesarean section

Postpartum

- Haemorrhage
- Pulmonary embolism, deep vein thrombosis
- Contraceptive failure

likely as nonobese women to be at risk of infertility and fail to become pregnant in both natural and assisted conception cycles.¹¹ Many obese women will have hyperinsulinaemia, elevated luteinising hormone (LH) levels, and associated ovulation disorder with low progesterone levels. Obese women are more likely to miscarry and there are a number of mechanisms that can play a role in this. Insulin resistance may inhibit normal corpus luteum function and impair progesterone production, which is fundamental in maintaining an early pregnancy. Obesity may also have a negative impact

HISTORY TAKING

- Age the biggest factor in determining pregnancy rates
- Coitus regularity and timing of intercourse
- Occupation/social circumstances are lifestyle issues reducing the frequency of intercourse?
- Ethnic background
- Obstetric history has she been pregnant before? Was there a delay in getting pregnant? Were previous pregnancies with the current partner? What were the pregnancy outcomes? Were there any antepartum/ intrapartum/postpartum issues?
- Gynaecological and obstetric history

 age at menarche, menstrual cycle regularity, dysmenorrhoea, menorrhagia, intermenstrual and postcoital bleeding, premenstrual spotting (a symptom of endometriosis), dyspareunia, sexually transmitted infections, contraceptive use (type and when ceased)
- · Pap smear history

on egg quality and an effect on endome - trial receptivity to embryo implantation.

Within assisted conception, overweight patients are more likely to have an abnormal response to ovarian stimulation. They may require higher doses of follicle-stimulating hormone (FSH) and have higher miscarriage rates and lower live birth rates.¹² Procedures such as oocyte retrieval are often more difficult and may result in lower retrieved egg numbers compared with women of a normal weight.¹³

An elevated body mass index (BMI) also has an effect on pregnancy outcome (see the box on this page).¹⁴ It is important to explain these potential complications to patients as often it motivates them to make positive lifestyle changes and to

- Breast history
- Family history taken from both partners, looking for conditions such as cystic fibrosis, physical or mental impairment, birth defects, recurrent miscarriage and clotting disorders. Disorders such as polycystic ovary syndrome and endometriosis have an hereditary component.
- General medical history body mass index, diabetes, cardiovascular and thyroid disease
- Surgical history especially intra-abdominal (e.g. complicated appendicitis, peritonitis)
- Psychiatric history
- Medications some medications can have negative impacts on fertility (e.g. NSAIDs can impair follicular rupture and ovulation)
- Allergies
- Social history alcohol intake/ smoking/recreational drugs
- Exercise/diet is she taking folate and iodine supplements?

lose weight. For these reasons, it is advisable to encourage patients to lose weight before conception and not during pregnancy. Again, GPs are in a unique position to facilitate this by referring patients to a specialist dietician or hospital-based metabolic/obesity unit. A realistic and regular program of exercise is also crucial.¹⁵⁻¹⁷

Bariatric surgery (laparoscopic gastric banding and related surgery) is becoming more popular in Australia as an effective, long-term solution to losing weight and maintaining ideal BMI. It is important to be aware that current evidence advises against conception within the first year of bariatric surgery due to an increased risk of miscarriage, fetal growth restriction and prematurity.¹³

TABLE. WHEN TO CONSIDER INVESTIGATIONS, REFERRALS AND LIKELY ACTIVE INTERVENTION

Female age	Investigations and referral	Likely active intervention, including assisted conception
Early 30s	12 months	18 to 24 months
Mid to late 30s	6 to 12 months	12 to 18 months
Late 30s to early 40s	6 months	6 to 9 months

Underweight women

At the other extreme, underweight women (BMI less than 20 kg/m²) are also likely to have difficulties conceiving as they may have chronic anovulation secondary to excessive exercise, stress and eating disorders. Low maternal weight is associated with adverse pregnancy outcomes including increased risk of miscarriage, preterm labour, intrauterine growth restriction and low birth weight.18,19 These patients should be counselled about the importance of adequate food intake and that pregnancy is best avoided until their BMI is normal. They may also require the assistance of a dietician and psychologist to achieve this goal. Overall, to avoid infertility secondary to menstrual disturbance, women should aim for a BMI between 20 and 25 kg/m² at conception.

INFERTILITY WORK-UP

Most couples will present with infertility after between six and 12 months of trying to conceive. In the early stages, (and before specialist referral) management can centre upon history taking (see the box on page 18), general education and a preconception screen. A careful history and examination can help identify a specific cause of female infertility and help tailor investigations and the need for referral.

As the history is taken, it is important to look out for red flags. Is there anything about the patient that would alert you to early specialist referral? Ensure both the female patient and her partner present in the consultation. A history from the male partner with regard to prior fertility, genital infections, surgery and general health is also important. The setting should be made comfortable and the interview prefaced by stating that personal questions will be asked.

Sex – timing and frequency

Questioning couples about intercourse can be challenging but is vitally important. There are many couples who for various reasons are not having intercourse and it is important to find out why and refer appropriately. Are there relationship issues/sexual dysfunction? If so it may be appropriate to refer the couple to a counsellor or sexual health physician. If intercourse is painful, this could signify pathology such as endometriosis and referral to a fertility specialist would be prudent.

Ovulation usually occurs about 14 days prior to menses. By convention the first day of menses is termed day one and therefore, a woman with a 28-day cycle, for example, will ovulate on about day 14. In contrast, a woman with a 32-day cycle will ovulate on about day 18. Particularly in the presence of a normal sperm count, sperm will remain healthy and viable for two days after intercourse. In contrast, following oocyte release, the egg will survive unfertilised in the fallopian tube for only a few hours. Therefore, couples should be encouraged to try every other day for the few days leading up to and overlapping the presumed day of ovulation.

It is important that patients are familiar with phases of the menstrual cycle, so that they are best advised of their fertile time.

- Follicular phase. This begins on day one of the cycle. FSH stimulates a cohort of developing follicles. One follicle becomes dominant and secretes oestradiol, which is the hormone paramount to endometrial development. Oestradiol also causes changes in cervical mucus to facilitate the passage of sperm through the cervix and into the uterus. Patients may note these mucus changes and this can help them to time intercourse.
- Ovulatory phase. The level of LH acutely rises in response to a number of factors including rising oestradiol levels. The LH surge enables final oocyte maturation prior to causing follicular rupture and release of the oocyte. Ovulation usually occurs 14 days before the next period is due.
- Luteal phase. The ruptured follicle becomes the corpus luteum. This structure primarily produces progesterone, the hormone required to make the endometrium 'receptive' to the embryo. Receptivity is vital for implantation to occur. Failed conception leads to cessation of corpus luteum function, a drop in progesterone levels and shedding of the endometrium leading to menstruation.

An awareness of these three phases enables the patient to better understand basal body temperature (BBT) charts and tests of LH surge (described below).

Basal body temperature chart

The BBT chart reflects the action of progesterone on thermoregulatory centres in the brain. Two days following ovulation, body temperature increases by a quarter to half a degree celsius. Over several months, BBT charts enable a

COMMON CAUSES OF FEMALE INFERTILITY

- Idiopathic age
- Endometriosis
- Tubal disease damage due to infection or disease such as endometriosis
- Ovulation disorders polycystic ovary syndrome, hyperprolactinaemia, hypothalamic anovulation due to stress, exercise, weight loss
- Uterine abnormalities fibroids and endometrial polyps, congenital anomalies of the uterus

retrospective view of when ovulation takes place in the cycle and hence help time when to have intercourse in future cycles. Although it is not a very efficient way to predict ovulation, BBT charting is simple and inexpensive. Core body temperature is best measured, for example, by placing the thermometer in the vagina.

LH testing

LH testing kits to detect the LH surge are a better way of predicting ovulation. A positive result means that ovulation will occur within the next day or so, enabling couples to plan intercourse. LH kits are relatively expensive because they can only be used once; however, if used with saliva testing to measure oestradiol levels, costs can be minimised. Rising oestradiol levels in the follicular phase cause ferning of mucus, including salivary mucus. Ferning can be used as a sign to start testing for the LH surge.

© ISTOCKPHOTO/AMANDA ROHDE **INVESTIGATIONS**

If couples are aware of their fertile time and are having regular intercourse, the next step in the management is to look for pathology. Given that female age is so crucial to the likelihood of achieving pregnancy, the time to undertake these

PCOS - A COMMON CONDITION IN INFERTILE WOMEN

Polycystic ovary syndrome (PCOS) is the most common cause of ovulation disorder in the community. The diagnosis is based on having two out of the following three criteria:20

- ultrasound diagnosis of polycystic ovaries (Figure 1)
- irregular or absent ovulation causing menstrual irregularity
- · clinical or biochemical evidence of androgen excess - excess hair growth.

acne, elevated levels of total testosterone.



Figure 1. Ultrasound showing polycystic ovaries.

Other conditions with similar signs as PCOS need to be ruled out, such as hyperprolactinaemia, thyroid disease, Cushing's syndrome and androgen secreting tumours.

A lipid profile, fasting insulin levels and a glucose tolerance test should be undertaken by women with confirmed PCOS.

PCOS may cause infertility and endometrial hyperplasia (related to unopposed oestrogen effect on the uterine endometrium) and has other metabolic consequences, so it is important to educate patients with PCOS about their condition and how it can be managed.

Many patients with PCOS will be overweight, so weight loss through prudent diet and exercise should be the first step in treatment as it may be enough to correct hormone imbalance, anovulation and associated metabolic consequences. Further management should be undertaken with the assistance of a fertility specialist.

investigations and to consider specialist referral is heavily dependent on female age (see Table). GPs can order most of the investigations outlined below. However, the AMH level may be better ordered by the fertility specialist as patient with a low antimullerian hormone (AMH) level may require specific counselling. Common possible causes of infertility are listed in the box on this page, with polycystic ovary syndrome (PCOS) being the most common cause of ovulation disorder (see the box on this page).²⁰

Blood tests

Preconception blood screen

Preconception blood screen should be performed in all women who want to conceive. This includes a full blood count, blood group, thyroid function tests, rubella, varicella, hepatitis B and C, and

HIV serology, and, depending on racial background, a thalassaemia screen.

Hormonal studies

Testing FSH and oestradiol levels on day one to three of a woman's cycle is used to measure ovarian reserve. As the cohort of oocytes that are responsive to gonadotrophin declines with age, declining negative feedback to the pituitary gland leads to an elevation of serum FSH levels. This test is only reliable if performed early in the menstrual cycle and if the oestradiol level is baseline (less than 200 pmol/L).

AMH is becoming a popular test of ovarian reserve. AMH is produced by the cells surrounding oocytes (granulosa cells) and measuring levels of this hormone at any time during the cycle has been shown to be a good predictor of the



Figure 2. Blocked fallopian tube shown on hysterosalpingography.

quantity, not quality, of a woman's egg reserve. The level of this hormone may assist with the speed of referral.

A progesterone assessment can be carried out to confirm ovulation. This should be performed during the mid-luteal phase at about day 21 if a woman has a 28-day cycle. If cycles are longer, measurement of serial progesterone levels may need to be performed.

If a woman's cycle is irregular and PCOS is suspected then further assessment, such as sex hormone binding globulin, total testosterone and free androgen index tests should be carried out. Prolactin levels should also be measured to exclude hyperprolactinaemia.

Imaging

Transvaginal ultrasound

If an anatomical problem involving the ovaries, uterus or fallopian tubes is suspected then a transvaginal ultrasound should be performed in the first two weeks of the cycle (follicular phase). This is to ensure that a corpus luteum will not be misinterpreted as a pathological cyst. The timing of an ultrasound is important as polyps or a truly thickened endometrium may not be seen during the secretory phase (second half of the cycle). Patients may need to have a repeat ultrasound if the timing is incorrect and this wastes time and resources.

HSG and HyCoSy

An assessment of the patency of the fallopian tubes can be performed as an outpatient using a hysterosalpingography (HSG) or hysterosalpingo-contrast-sonography (HyCoSy). Both procedures involve placing a catheter into the cervix to infuse dye/ contrast into the uterus. Flow is then observed along the fallopian tubes. The HSG is a radiological procedure (Figure 2) whereas the HyCoSy is a transvaginal ultrasound procedure. There is a potential benefit of HyCoSy over HSG in that it allows simultaneous assessment of ovarian/adnexal and uterine anatomy with ultrasound as well as testing for tubal patency. In contrast, an HSG provides superior views of the interior uterine cavity and of the internal structure of the fallopian tubes. The latter may be ordered if there is suspicion of tubal damage (such as in a woman with a history of prior *Chlamydia* infection).

Both HyCoSy and HSG should be performed in the first 10 days of a woman's cycle and the patient should be informed of the discomfort associated with both of these tests. It is important that patients take analgesia (preferably a NSAID) one hour before the procedure.

HSG and/or a two-dimensional ultrasound can be used as an initial screening tool if a uterine anomaly is detected or suspected. Recent reports suggest that a three-dimensional ultrasound has a very high accuracy rate in diagnosing uterine anomalies,²¹ which can be associated with recurrent miscarriage and in some cases can be surgically corrected. For example, the removal of a uterine septum will potentially decrease the risk of miscarriage and preterm birth. The prevalence of congenital uterine anomalies has been reported as 6.7% in the general/ fertile population, 7.3% in the infertile population and 16.7% in the recurrent miscarriage population.²¹

Laparoscopy with dye instillation

Laparoscopy with dye instillation remains the gold standard of fallopian tube assessment; however, because this is an invasive and expensive method of assessment, it is not the preferred firstline option. Laparoscopy is generally indicated in women with findings on imaging, unexplained infertility and pelvic pain or other symptoms suggestive of endometriosis.

Hysteroscopy

A hysteroscopy is the most definitive method for evaluating the uterus but, similar to laparoscopy, is more costly and invasive than imaging studies.

MRI of the brain

A MRI of the brain is indicated if persistent hyperprolactinaemia is noted and a pituitary tumour needs to be excluded. Rarely, unexplained amenorrhoea can be secondary to a nonprolactin-secreting pituitary tumour or other intracranial lesion.

Tests no longer used

A postcoital test, which assesses the interaction between cervical mucus and sperm, is no longer commonly performed. This is due to complexities of timing and the indirectness of the limited information it provides. Adding to this is the fact that many couples would proceed to treatments such as IVF irrespective of the result.²²

TESTING THE MALE PARTNER

Although male infertility is beyond the scope of this article, it is essential to take a history from the male partner and to examine him. Semen analyses are often performed poorly, so ask your fertility specialist to recommend a trusted laboratory before ordering this test.

SUMMARY

Female infertility is a common problem and the GP should be able to elucidate potential causes by efficient history taking and performing initial investigations as appropriate. Key lifestyle issues such as obesity should be addressed and the patient informed about the impact of such issues on fertility and pregnancy. GPs have the privilege of regular patient review and rapport and can use their position to remind women, once every so often, of their biological clock. It is prudent for the GP to refer an infertile couple to an infertility specialist early to maximise the couple's chance of conception. MT

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COMPETING INTERESTS: Dr Andreadis: None. Dr Bowman is a shareholder in Sydney IVF Ltd and had held positions on advisory boards for Merck-Serono and MSD. He has received educational grants from these companies.

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