The infertile couple
assessment and treatment options

GPs are ideally placed to undertake the initial work up of couples who are being investigated for infertility.

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Infertility is a medically important disability affecting more than 15% of couples trying to have a baby. This figure is increasing as couples delay starting a family until the woman is in her late thirties, or even forties.

The goals of a medical evaluation of infertility are to:
- find a cause
- present a realistic prognosis
- provide options for treatment.

To do this meaningfully involves educating the couple on their normal reproductive physiology and providing an explanation of how, or why, this is going wrong.

When to investigate

Couples and their doctors should appreciate that it usually takes some time to achieve pregnancy. For women aged between 25 and 35 years, there is on average a 20% chance of becoming pregnant in each ovulatory cycle. Roughly 85 to 90% of couples in this age range will achieve a pregnancy in the first year of attempting conception. For younger women the monthly probability of pregnancy is higher, and for older women it can be much lower; however, 12 months of trying unsuccessfully to conceive is the often-used benchmark for infertility at any age. Thus this is the time at which assessment of couples for infertility is indicated. Earlier assessment may be warranted if there are clinical clues to probable abnormal reproductive function, such as:
- irregular or absent menstrual periods
- significant pelvic symptoms suggestive of pelvic adhesions or endometriosis
- a history of scrotal injury or surgery
- advanced female age (e.g. over 38 years).

The initial assessment

Whenever possible both partners should attend the initial consultation. Infertility is a disability that takes, and affects, two people. Essential details to be noted from the couple's history include:
- age
- previous pregnancies in this and earlier relationships

IN SUMMARY

- **The number of couples seeking advice on infertility is increasing, as treatment options improve and as women postpone starting a family.**
- **Assessment of infertility should generally begin if a couple has failed to conceive after one year or more of regular unprotected intercourse; investigation should start earlier if there are firm clinical indications of underlying pathology.**
- **GPs can perform initial investigations, focusing on tests of ovulation, sperm production, tubal patency and uterine structure.**
- **These investigations can distinguish between sterility (i.e. no chance of getting pregnant without help) and subfertility (i.e. some hope of pregnancy without treatment).**
- **The treatment of infertility can be cause-based (the more clear cut the cause, the more effective its correction will be) or 'symptomatic' (when IVF is used to secure the wanted pregnancy more directly) .**

- time spent attempting conception
- previous genital or pelvic infection, pelvic or inguinal surgery, injury or infertility investigations.

For women it is important to note:

- the duration and periodicity of menstruation (increasingly heavy periods indicate pelvic pathology such as fibroids, endometriosis or adhesions; a long or irregular cycle suggests a disorder of ovulation)
- previous contraceptive use – e.g. intrauterine contraceptive devices, oral contraceptives, depo-progestogens (depo-progestogens may cause a delay to conception of up to nine months after the last injection owing to suppressed menstrual function; suppressed function beyond 12 months is not due to this drug and warrants further evaluation)
- any premenstrual spotting or increasing dysmenorrhoea (either of which is predictive of endometriosis)
- the starting date of the last menstrual period, both to consider whether the woman might already be pregnant and to time tests for when they are most informative.

If there are indications of sexual dysfunction it may be better to explore the symptoms with each of the couple separately and privately. We find a good time to do this is with one partner in the office while the other is preparing him or herself for examination in the adjacent consulting room.

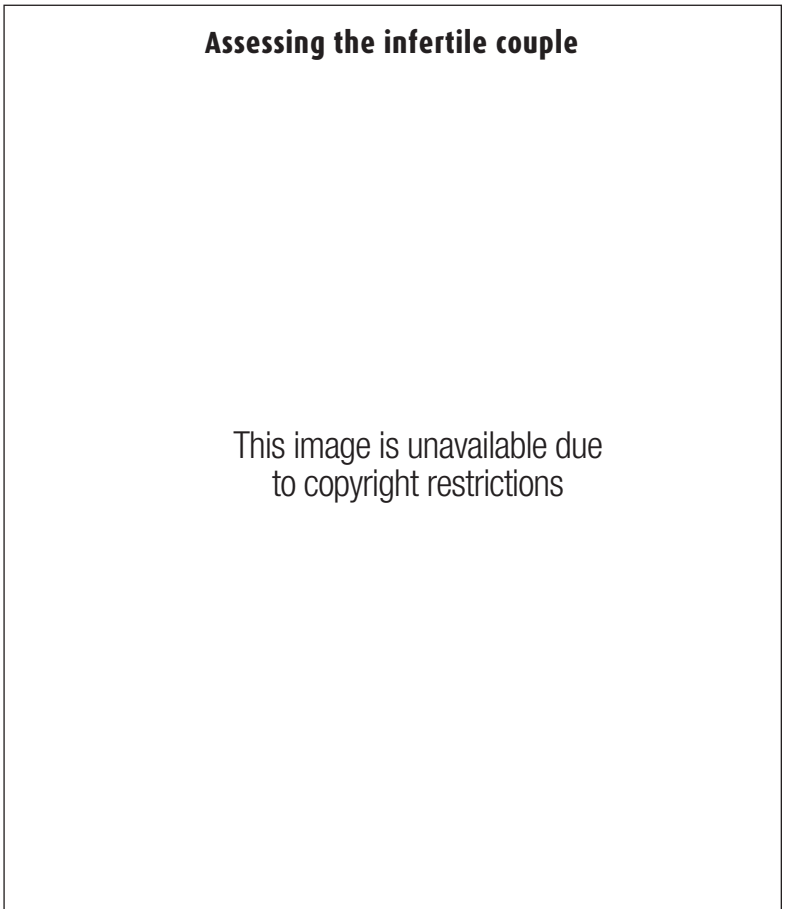
The value of the examination will depend on the experience the practitioner has had with pelvic and scrotal examinations.

The GP's role

GPs providing the initial work up for infertility are uniquely placed to discuss issues pertaining to pregnancy where early intervention can be critical. Certain opportunistic screening can be undertaken and advice provided on lifestyle, nutritional status and vitamin supplementation. Routine tests should be conducted if they have not already been done, including:

- Pap smear
- breast check
- assessment of rubella immunity and hepatitis B and hepatitis C status
- perhaps, testing for syphilis and HIV.

Assessing the infertile couple



Assessment of infertility is generally indicated in couples who have not conceived after 12 months of regular, unprotected intercourse. Earlier assessment may be warranted if there are clinical clues to abnormal reproductive function.

Women should be advised to take folic acid supplements for at least one month before trying to conceive. A daily dosage of 400 to 500 μg is recommended, although there is increasing evidence that 5 mg/day is even more effective in preventing neural tube defects. Folic acid supplementation should continue during the first 12 weeks of pregnancy.

Both partners should be advised to give up smoking. Women with a BMI greater than 30 kg/m^2 should be counselled on undertaking a supervised weight loss program.

Investigating the causes of infertility

For conception to occur:

- eggs need to be ovulated

- sperm need to be ejaculated
- an egg and sperm must meet for fertilisation
- the early embryo must attach to, and implant in, a receptive uterus.

The tests available to the GP can begin to explore these four circumstances very effectively.

Ovulation

Short of pregnancy, the evidence that an egg is released by the ovary each month is circumstantial. Regular, slightly painful periods usually imply regular ovulation. An elevated serum progesterone level a week before an expected menstruation offers practical confirmation. The single serum progesterone sample is timed for the middle of the luteal phase (the two-week-long second half of the cycle, defined by the presence of a recently formed corpus luteum) – i.e. day 21 of a 28-day cycle (Figure 1). For cycles that are longer or shorter, it is much more likely to be the preovulatory follicular phase that has varied than the luteal phase. A properly timed serum progesterone level confirming ovulation should exceed 30 nmol/L.

If anovulation is suspected or confirmed, additional tests may be arranged to ascertain the cause of the ovulatory dysfunction before the patient is referred to a specialist. These tests include thyroid function tests and measurements of serum prolactin level, serum unbound androgens (such as a free androgen index or a serum free testosterone), and serum follicle stimulating hormone (FSH) and luteinising hormone (LH) levels. If the woman is menstruating, FSH and LH should be measured during the period.

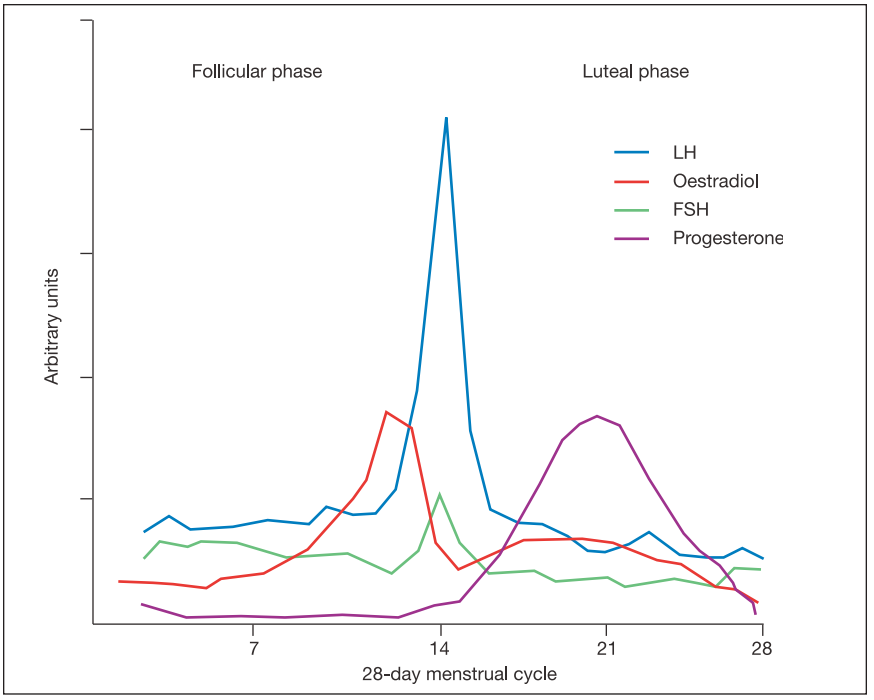


Figure 1. Schematic representation of the sequence of hormone rises during an ovarian cycle. The small FSH rise at the start of the cycle initiates follicle growth; oestradiol rises as follicles respond. The LH surge triggers ovulation, then progesterone increases as the corpus luteum forms, potentially to support early pregnancy.

Sperm production

Any pathologist can perform a semen analysis on a specimen that has been collected by the patient at home. The semen sample should be obtained after two or three days' abstinence from ejaculation. The sample should be produced by masturbation, not by coitus interruptus or by using a condom (ordinary condoms are spermicidal). Inform the patient to keep the semen sample at room temperature and take it to the laboratory within an hour of collection.

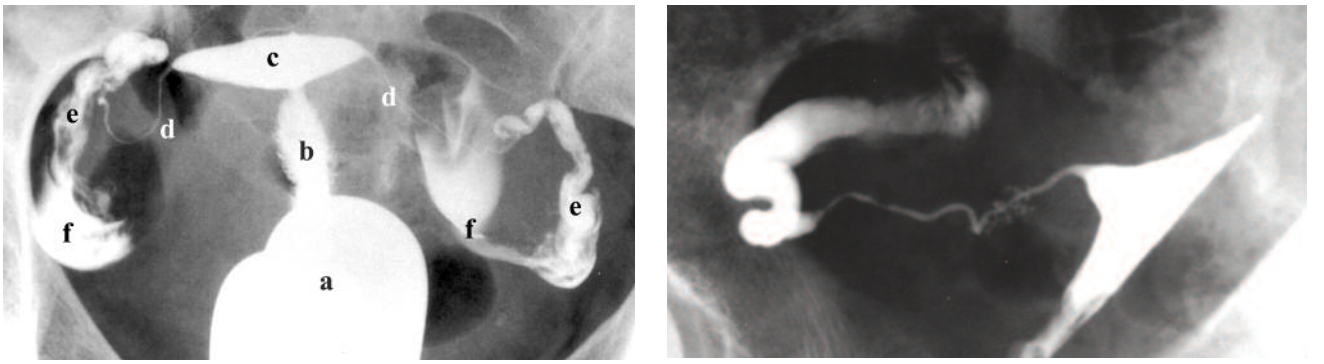
Table 1 lists normal semen parameters.

Table 1. Normal semen parameters

Volume of ejaculate	≥2 mL
pH	7.2 – 7.8
Density	≥20 x 10^6 sperm/mL semen
Motility	≥50% mobile sperm or ≥25% with rapid progression within one hour of ejaculation; a 'motility index' >120/300
Morphology	≥30% morphologically normal sperm; a 'teratozoospermia index' <1.8

Tubal patency

The most reliable test for tubal patency short of an operative laparoscopy (which would require specialist referral) is a hysterosalpingogram (HSG; Figures 2a and b). Precautions are necessary because pre-existing salpingitis can be exacerbated, especially if one or both tubes are blocked at their distal, outer end.



Figures 2a and b. a (left). A normal hysterosalpingogram: a=speculum in the vagina; b=cervical canal; c=endometrial cavity; d=tubal isthmus; e=tubal ampulla; f=spill of contrast out of the fimbrial end, among the intestines. b (right). A hydrosalpinx seen on the hysterosalpingogram can cause sterility even if it is unilateral. From: Jansen R. Getting pregnant. Sydney: Allen & Unwin; 2003, with permission.[1]

If there is a history of pelvic inflammatory disease the risk of reinfection following HSG is high, so the patient should be referred to a specialist for laparoscopy. Similarly, if masses or tenderness are elicited during pelvic examination or endometriosis is suspected, a laparoscopy, not HSG, should be performed. Abnormalities of the pelvic organs, particularly endometriosis or pelvic adhesions (which may be affecting a couples' monthly conception chance), can be diagnosed laparoscopically. Tubal dye studies performed in conjunction with laparoscopy enable assessment of tubal patency status.

A noninvasive screening test for previous chlamydial salpingitis (by far the most common cause of tubal disease) is measurement of serum chlamydial antibody levels. Although the presence of these antibodies does not confirm damaged tubes, their absence rules out previous chlamydial pelvic infection.

A receptive uterus

A transvaginal ultrasound of the uterus and ovaries performed in the midfollicular phase (on about day 7 after the start of menstruation) is a cost effective way to provide much information (Figures 3a to c). Specifically, the endometrium should be more than about 5 mm thick but still essentially nonreflective (echolucent) to ultrasound. A thick, echogenic endometrium at this stage indicates endometrial hyperplasia, or an endometrial polyp if it is present in the follicular phase. This is enough to account for infertility. This is a good time also to visualise fibroids.

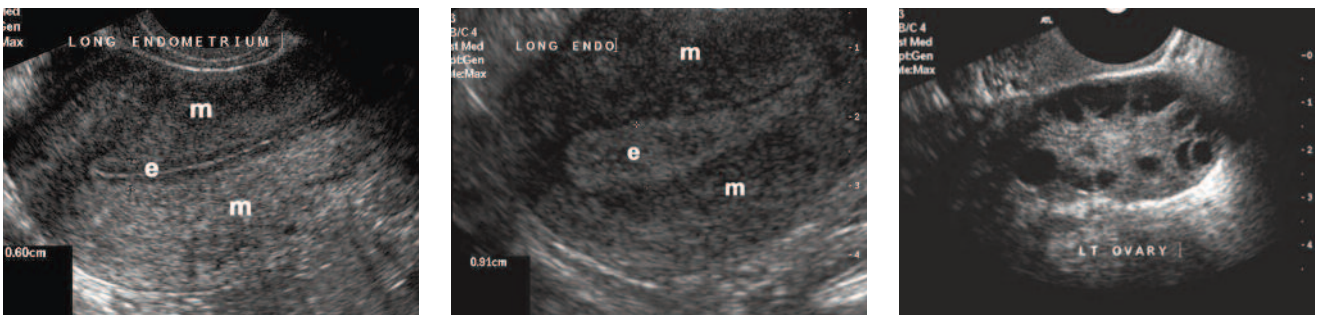
In the ovaries, follicular recruitment will be advanced by day 7 but follicular competition and atresia of all but the eventually dominant follicle will not yet have begun. This makes it possible to anticipate the number of follicles likely to respond to FSH in preparation for egg retrieval in a future cycle.

Moreover, at this stage an echogenic cyst can be identified as an endometrioma. In a scan taken after ovulation it can be difficult to distinguish between an endometriotic cyst and a cystic corpus luteum that contains blood.

Occasionally, the scan reveals a forgotten intrauterine device.

Interpreting abnormalities

If abnormalities detected are total – i.e. there are no eggs or sperm, or there are



Figures 3a to c. Transvaginal ultrasounds on day 7 of the cycle: e=endometrium; m=myometrium. a (left). Normal: the endometrium is thin and rather echolucent. b (middle). Abnormal: the endometrium is thickened and echogenic, an appearance that would be normal in the secretory (luteal) phase but not at day 7. c (right). An ovary showing multiple early follicular development.

completely blocked tubes or is no uterus – there is 'sterility', and no chance of achieving pregnancy without major intervention. When one of these parameters is abnormal, but not total, there is 'subfertility', and management can be more difficult to define. Tables 2 and 3 summarise the main causes of sterility and subfertility, respectively.

Once initial evaluation is complete, referral of the couple to a specialist is recommended.

Options for treatment

Treatment of the infertile couple depends on the problems identified and the willingness and ability of the couple to undergo the necessary procedures. There is often a choice between rectifying the underlying abnormality or skirting the diagnosis and relying on assisted conception technology, including IVF. These two approaches are not necessarily mutually exclusive. The box on page 24 provides some definitions for assisted reproductive techniques.

Sperm disorders

Effective treatment aimed at improving semen parameters is unusual. Treatment often takes the form of assisting conception with timed intrauterine insemination or IVF, if necessary using intracytoplasmic injection of a single sperm into the egg (ICSI), which has revolutionised treatment. Even cases of azoospermia can be treated more often than not, either by aspirating sperm from the epididymis proximal to an obstruction or by aspirating immature sperm directly from testicular tubules in many cases of nonobstructive azoospermia. Otherwise, donor insemination may be available.

Obstructive azoospermia is usually marked by normal levels of serum FSH, whereas primary testicular failure tends to produce an elevation of serum FSH. Rarely, testicular failure is secondary to low levels of FSH due to a pituitary tumour or it is congenitally acquired.

Ovulation disorders

With the exception of primary ovarian failure (an absence of ovarian follicles with an elevation of serum FSH), ovulation disorders are among the most treatable causes of infertility. The three common treatable causes are:

- polycystic ovary syndrome (PCOS), when there is an increase in the free androgen index or the serum unbound testosterone level, plus a visible accumulation of follicles around the

Table 2. Sterility: main causes and what to do next

Diagnosis	What next?
No sperm (azoospermia)	Distinguish obstruction from poor production; exclude genetic causes that can cause similar or other serious disease in offspring
No eggs (anovulation)	Distinguish primary ovarian failure (elevated serum FSH) from anovulation due to insufficient FSH
No open fallopian tube	Distinguish obstructions close to the uterus from those at the outer end; even a unilateral hydrosalpinx can cause sterility
No uterus, cervix, or endometrium (amenorrhoea despite ovulation)	If the uterus is present, determine the extent of endometrial atrophy

Table 3. Subfertility: deficiencies and explanations

Deficiency	Problem	Explanations
Sperm	Not enough sperm reach the fallopian tube	Oligospermia, sperm antibodies (male)
Cervix	Sperm transport disrupted	Cervicitis, previous cone biopsy, sperm antibodies (female)
Eggs	Eggs not ovulated normally or frequently	Oligomenorrhoea, luteal phase defect, early ovarian failure
Fallopian tubes	Sperm and eggs meet infrequently	Peritubal adhesions, incomplete blockage
Implantation	Weak embryos, or uterus not fully receptive	Oopause,* endometritis, fibroids, endometrial polyps
Mixed	More than one of the above	Includes endometriosis
Unexplained	Apparently none of the above	Natural genetic variation, effects of woman's age*

* Oopause: the metabolic weakness of eggs as women get older, while menstrual cycles are still regular, manifests as unexplained infertility until IVF is performed. Then it becomes apparent that embryos resulting from the eggs are not implanting successfully. Sooner or later this normal age-related development effectively becomes sterility.

periphery of the ovaries on ultrasound
- hypothalamic depression, when there are low androgen levels and low to normal serum FSH and LH levels; a disorder often contributed to by a low body weight and excessive exercise
- hyperprolactinaemia, or high levels of serum prolactin.

After exclusion of a pituitary tumour on MRI or CT scanning, hyperprolactinaemia is treated specifically with a dopamine agonist such as bromocriptine or cabergoline (Dostinex). Otherwise in cases of anovulation the first approach is generally to use clomiphene (Clomhexal, Clomid, GenRx Clomiphene, Serophene), an orally effective antioestrogen that acts by causing a temporary increase in FSH output. The oral hypoglycaemic agent, metformin, which sensitises tissues to insulin and insulin-like growth factor (IGF), can help improve response to clomiphene in cases of PCOS (IGF is an important paracrine factor in ovarian follicular response).

Women with more severe ovulatory disorders need treatment with injections of FSH (to grow follicles over about two weeks) and then human chorionic gonadotrophin (to mimic the midcycle surge of LH and ovulate the egg or eggs). Close monitoring with repeated measurements of serum oestradiol and transvaginal ultrasound to estimate the number and size of responding follicles is essential. Despite this there is a high risk of multiple pregnancy, and in many cases it is more prudent to perform egg retrieval and IVF, enabling restriction of the number of embryos transferred.

Definitions used in assisted reproduction

IVF
In vitro fertilisation: eggs are retrieved either transvaginally or laparoscopically from the ovaries, usually after stimulating the ovaries with injections of FSH. The eggs are fertilised in the laboratory and then transferred laparoscopically to the fallopian tubes on the first or second day after retrieval or, more typically, to the uterus three to five days after egg retrieval.

ICSI
Intracytoplasmic sperm injection: a variant of IVF that is effective for men with extremely low sperm counts.

TESE
Testicular sperm extraction: the direct removal of a few sperm from the tubules of the testis to enable ICSI in patients with very low sperm production.

MESA
Microscopic epididymal sperm aspiration: sperm are obtained from above the site of a blockage in the epididymis or in the vas deferens.

GIFT
Gamete intrafallopian transfer: a procedure now largely obsolete in which prepared sperm and eggs are placed in one or other fallopian tube for conception. Fertilisation takes place in the fallopian tube with natural selection of sperm occurring in the tube environment as happens with unassisted conception cycles.

IUI
Intrauterine insemination: the placement of 'washed' or prepared sperm through the cervix.

OHSS
The ovarian hyperstimulation syndrome: a potentially dangerous complication that can occur about a week after egg retrieval for IVF.

Fallopian tube disorders

The advent of IVF, which bypasses the fallopian tube anatomically and functionally, has revolutionised the prognosis in women with seriously damaged fallopian tubes. Previously such women could be treated only with painstaking, yet often inadequate, microsurgical repair operations.

Ironically, there is evidence that IVF is less effective in women in whom there is a total absence of fallopian tubes. This is certainly true if there is a hydrosalpinx, even a small one. In this case there is likely to be a release of fluid from the tube into the endometrial cavity at about the time an embryo enters the uterus, either from a contralateral normal tube or by placement into the uterus after IVF.

Uterine disorders

Abnormalities of the uterus are likely to affect equally natural conception or conception with IVF. Treatable causes include an endometrial polyp or a submucosal or major intramural myoma, or fibroid. Less treatable causes are intrauterine adhesions or endometrial atrophy from infective complications of pregnancy, such as curettage for a missed abortion or secondary postpartum haemorrhage.

In the absence of a uterus, IVF can still be used to produce embryos, but gestational surrogacy, in which a friend or relative becomes pregnant with the embryos, is the only way a woman can have a child that genetically is her own. IVF for gestational surrogacy is not reimbursed by Medicare, and surrogacy itself

is illegal in some States and Territories.

Endometriosis

Sometimes enigmatic, endometriosis is capable of altering the pelvic environment and contributing to subfertility through diverse disruptions of normal physiology. Treatment consists of destroying or removing lesions if they are discrete, or ignoring them and proceeding with IVF. Suppression with hormonal drugs stops ovulation and is not efficacious for infertile women.

The success of IVF is not reduced in women with endometriosis unless:

- a major part of the ovaries has been excised during attempts to treat ovarian endometriosis
- a hydrosalpinx has resulted from an endometriotic stricture or inadvertent postoperative adhesions from previous surgery.

Immunological infertility and cervical disorders

Sometimes a localised disturbance in cervical mucus that blocks normal sperm penetration can be overcome with timed intrauterine insemination of prepared sperm. If not, IVF is generally effective. (Local disturbance may include sperm antibodies in either the cervical mucus or the semen. Sperm antibodies result from an immune response against sperm cells.)

Mild but multiple disorders and 'unexplained' infertility

Generally the more obvious or serious the cause, the more likely it is that correcting it will result in pregnancy. Conversely, when no cause can be identified, only the passage of time (perhaps) or the use of IVF will work. The longer the duration of the infertility, the worse the prognosis and the more likely that IVF will be needed. If time is short due to advancing maternal age, IVF should be started sooner rather than later.

When there are multiple causes of infertility, it can be difficult to remedy one without risking exacerbating another. For example, the use of clomiphene for an ovulation disorder when the sperm count is poor makes it more difficult for sperm to reach the fertilisation site owing to the antioestrogenic effect that clomiphene can have on cervical mucus. In many of these complex cases IVF skirts the pathology, producing standard success rates.

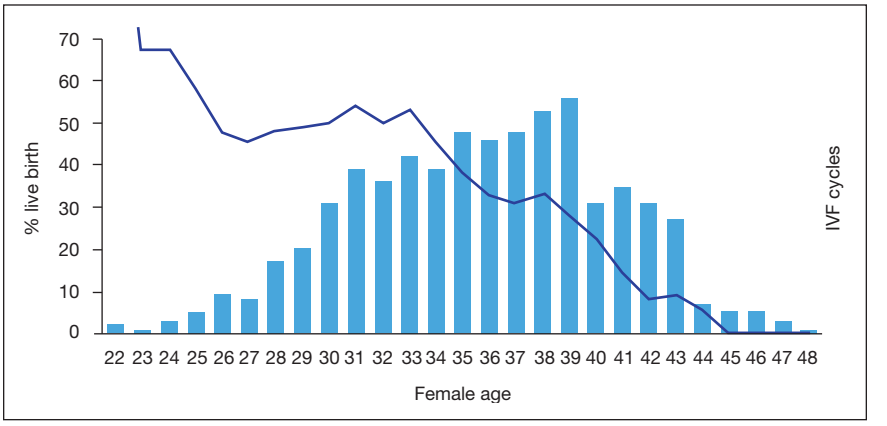


Figure 4. IVF treatments performed in women at Sydney IVF in 1998 according to age (bar chart; right axis) and the effect of female age on the chance of a live birth from one IVF treatment (line graph; left axis). Generally these results are obtained with the transfer of just one embryo at a time, up to the age of 38 years in women having their first IVF treatment. Up to the age of the mid-thirties, the chance of a baby from one round of IVF is now about 50%. Adapted from Jansen, 2003.[1]

Advanced maternal age

IVF does not compensate for the inexorable decline in fertility that starts, on a population basis, from about the age of 35 years (Figure 4). For individuals, this decline can be more abrupt and can precede the menopause by up to 10 years. We refer to this phenomenon as the oopause: a physiological cessation of fertility well before there is any loss of the normal oestrogen-producing functions of the ovary. There are no tests for it short of IVF.

Dispelling some myths

Reassure couples that:

- a moderate amount of alcohol, such as a glass or two of wine, appears to improve fertility
- they can have sex as often as they want to; although sperm density might fall slightly when ejaculation is frequent, all other important sperm parameters improve. In addition, it has been shown that conception rates are higher with daily sex than with second daily or less frequent sex.

Conclusion

In the assessment of couples for infertility, GPs are ideally placed to perform initial investigations, focusing on tests of ovulation, sperm production, tubal patency and uterine structure.

Treatment options for infertile couples are usually aimed at either rectifying the underlying abnormality or by-passing the diagnosis and relying on assisted conception technology, including IVF. With the techniques currently available, many couples can attempt and achieve a pregnancy. MT

Reference

1. Jansen R. Getting pregnant. Sydney: Allen & Unwin; 2003.

DECLARATION OF INTEREST: None.