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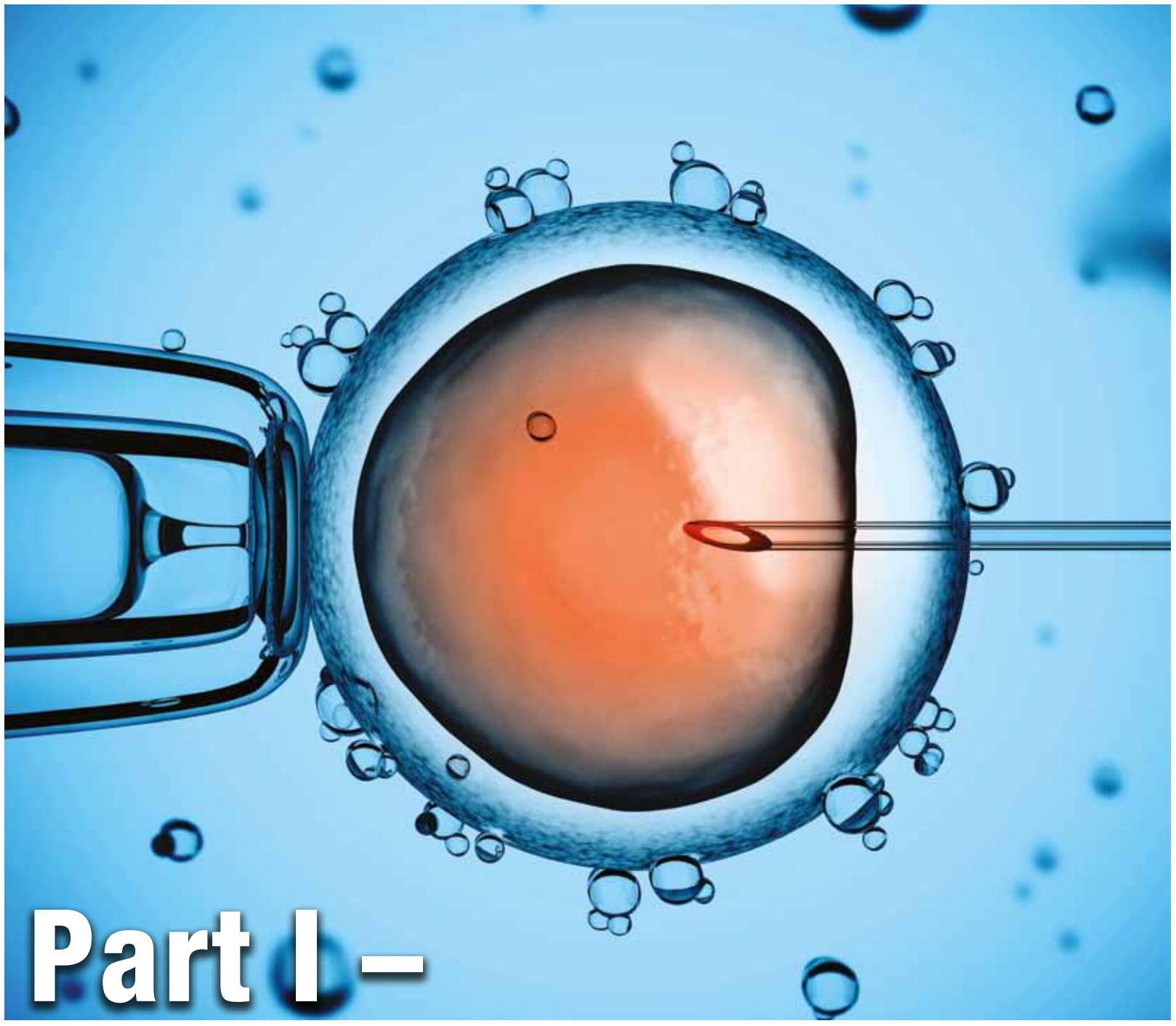

Part I – SUBFERTILITY and IVF

Introduction

THE world's first IVF baby was conceived in 1977 on the 102nd attempt by Steptoe and Edwards. Five million have followed.[1] IVF has become a common solution for many fertility problems because of it 'short circuiting' the complex processes leading to natural conception.

The WHO definition of infertility as a failure to conceive after a year of unprotected intercourse encourages a dichotomous view of fertility.[2] A couple is deemed either fertile or infertile, conflicting with the fact that absolute sterility is relatively uncommon. The probability of conceiving within a certain time frame is a more relevant consideration and is influenced by factors such as female age and sperm quality. Subfertility is a reduced probability of conceiving and therefore both a prognosis and diagnosis. It is vital to ensure appropriate management takes place before declining egg quality renders all strategies useless, excepting adoption and donor-egg IVF.

Many subfertile couples ultimately fail to conceive because they drop out of treatment while there is still a good chance of success. The challenge is to keep couples on a steady course during a time of great emotional strain.

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INSIDE

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Physiology overview

Reproductive physiology

THE pathway to success involves complex biological events (eg, meiosis) that can go awry at the earliest stages. A large percentage of early human conceptions are aneuploid (30-60%) and will not progress, ending imperceptibly or as slightly late menses. A subset of these will become clinical miscarriages, and a few, mainly trisomy 21, will result in live births.

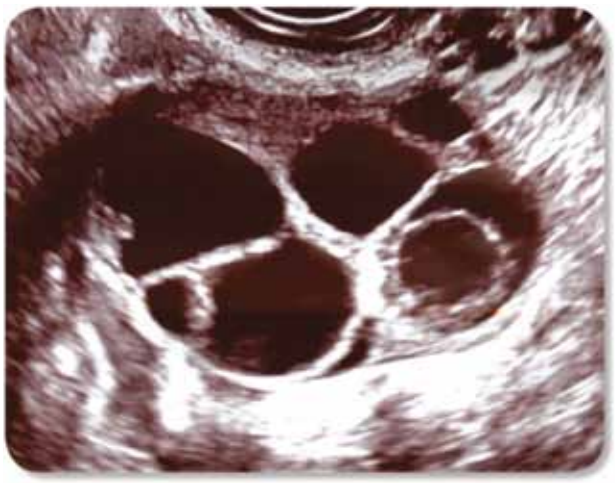
A brief overview of some of the key elements of natural fertility:

- Oocytes destined to be involved in a cycle are recruited 10 weeks prior. Artificial superovulation, therefore, does not 'waste' eggs or hasten menopause. While all oocytes have been present since mid-fetal life, the male makes spermatozoa on a 72-day cycle.
- Follicles progress from microscopic dimensions to an impressive 2cm diameter if ovulatory. During an ovulatory cycle, a cohort of 5-20 follicles commences development. Through complex feedback loops, involving FSH from the pituitary and oestrogen from follicles, usually only one follicle will reach ovulation.

Table 1: Spontaneous conception rates

Age	Spontaneous conception rate
Early 20s	25% per cycle
Early 30s	19% per cycle
35 years	15% per cycle
39 years	8% per cycle
45 years	1% per cycle

Source: Lyttleton S. The infertile couple. *O and G magazine* (RANZCOG) 2010; 12(3):28.



Ultrasound of ovary showing follicles.

- Ovulation occurs about 34-36 hours following a surge in LH from the pituitary. A regular 25-35-day menstrual cycle usually implies oocyte release from the ovary regardless of signs and symptoms. The post-ovulation follicle becomes the corpus luteum. This secretes progesterone, preparing the endometrium for implantation.
- Spermatozoa survive in the genital tract for up to seven days, with good fertilisation potential in the first 2-3 days. Fertilisation takes place within the fallopian tube, and the resulting zygote rapidly divides and becomes a blastocyst, implanting about six days post-fertilisation.

Physiology of IVF

The aim of IVF is to mature a number of ovulatory follicles by interfering with the mechanism that normally leads to just one dominant ovulatory follicle. Daily injections of FSH are commenced at the start of the cycle to stimulate a group of follicles, with a secondary medication (gonadotropin-releasing hormone agonist or antagonist) introduced to down-regulate the hypophyseal–pituitary axis. This prevents an early LH surge and allows the entire cohort of follicles to achieve maturation. A single trigger injection of a drug capable of instigating or mimicking an LH surge is given 35-36 hours ahead of egg collection. Eggs are then collected transvaginally from large preovulatory follicles by ultrasound-guided aspiration and are placed with prepared spermatozoa to allow for 'natural fertilisation'.

Alternatively, sperm can be selected and microinjected directly into the oocyte, intracytoplasmic sperm injection (ICSI). Resulting embryos are cultured for 3-5 days while the endometrium is supported with human chorionic gonadotropin injections to maintain the corpora lutea or directly with progesterone pessaries. A single embryo (very occasionally two) is then transferred into the uterus via the cervix. Any spare embryos of apparent good quality are frozen.

Pathophysiology of infertility

Reproduction involves (1) the release of a normal preovulatory oocyte, (2) production of adequate spermatozoa, (3) normal transport of gametes to the fallopian tube for fertilisation, (4) transport of the cleaving embryo into the endometrial cavity and (5) implantation and development. Any disruption of these steps affects fertility.

Causes of subfertility

OVARIAN dysfunction, male factor, unexplained, and combinations of the first two categories are common causes. Pelvic pathology, such as endometriosis and fibroids, can have variable degrees of significance. Bilateral tubal obstruction and azoospermia are relatively uncommon (see tables 2 and 3).

In the absence of an overt cause for infertility, there are multiple potential factors, which are difficult to quantify in terms of degree or significance. Investigations should be performed on a reasonable basis.

Age, fertility and IVF success rates

Over the past half century, increasing numbers of Australian women in their late 30s and early 40s have been seeking fertility assistance, reflecting the trend for couples in affluent countries to delay starting families. Men's fertility also declines with age but not nearly to the same degree.

From birth to menopause, oocytes decline from one million to one thousand. There is also a reduction in oocyte functionality with ageing. Mitochondrial function gradually declines, reducing metabolic capacity, and an increasing incidence of aneuploidy is observed from failure of paired chromosomes to separate in meiosis (non-disjunction).

Studies of populations where marriage occurs at a young age and no contraception is used show that half the female population cease producing babies after the age of 40. In IVF, this decline is also observed (see figure 1).

Interpreting and auditing IVF success rates can be difficult. Results reflect clinic quality, patient cohort and methods of analysis. Success rates can be expressed as clinical pregnancies per transfer (ie, fetal heart activity on ultrasound), the more relevant 'live-birth' rate per transfer and pregnancies per egg collection, which includes subsequent frozen transfers and reflects the IVF clinic's ability to freeze embryos. There are wide differences between Australian clinics (eg, the live-birth rate of fresh cycles for women under 35 in 2012 in different units ranged from 5.4% to 38.6%).[3]

Table 2: Causes of reduced female fertility or sterility

Ovulation disorders (common):
Advanced age — reduced reserve/oocyte function
Diminished ovarian reserve (any age)
Endocrine disorder (eg, hypothalamic amenorrhoea, hyperprolactinaemia, thyroid disease)
Polycystic ovary syndrome
Toxins (eg, tobacco, chemotherapy)
High/Low BMI and extreme exercise
Tubal factors (prevalence varies):
Obstruction (eg, history of pelvic inflammatory disease, tubal ligation)
Endometriosis (particularly if severe)
Other (about 10%)
Uterine/Cervical factors (more than 3%):
Congenital uterine anomaly
Fibroids (dependent on nature)
Endometrial polyps
Poor cervical mucus and antisperm antibodies
Uterine synechiae

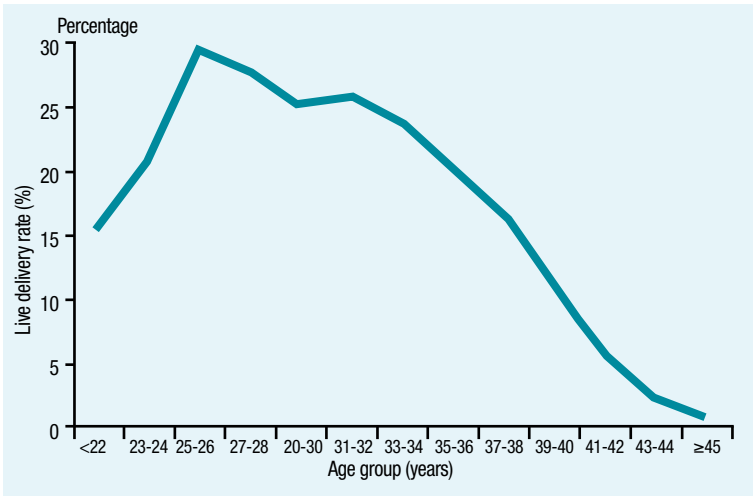


Figure 1: Australian and New Zealand age-specific live delivery rates per initiated fresh cycle by two-year age groups. Women in their mid-20s to mid-30s had the highest live delivery rates. This rate steadily declined for women older than 32. For women 45 years or older, only one live delivery resulted from every 100 initiated cycles. This is in comparison with 25 deliveries per 1000 initiated cycles in younger women (25 – 34 years). (Source: Macaldowie A, Wang YA, Chughtai AA & Chambers GM 2014. *Assisted reproductive technology in Australia and New Zealand 2012*. Sydney: National Perinatal Epidemiology and Statistics Unit, the University of New South Wales).

Table 3: Causes of reduced male fertility or sterility

Unknown (common)
Obesity
Advanced male age
Primary hypogonadism (common):
Androgen insensitivity
Congenital or developmental testicular disorder (eg, Klinefelter syndrome, Noonan syndrome)
Cryptorchidism
Medication (eg, alkylating agents, ketoconazole, Salazopyrin)
Orchitis, including mumps orchitis
Radiation
Systemic disorder (eg, haemochromatosis)
Testicular trauma
Varicocele (controversial)
Y chromosome defect/microdeletion
Altered sperm transport (occasional):
Absent or obstructed vas deferens
Epididymal absence or obstruction
Erectile dysfunction
Retrograde ejaculation
Secondary hypogonadism (uncommon):
Androgen excess state (eg, tumour, exogenous administration — becoming more common)
Congenital idiopathic hypogonadotropic hypogonadism
Hyperprolactinaemia
Infiltrative disorder (eg, sarcoidosis, TB)
Medication (eg, antiandrogens, spironolactone)
Multiorgan genetic disorder
Oestrogen excess state (eg, tumour)
Pituitary disorder
Secondary adrenal tumour
Testiular trauma
Thyroid disease

Initial assessment

History

AN estimation of the probability of conception in the ensuing 12 months will dictate overall strategy and reduce the common problem of fertility management: too much too soon or too little too late. Establishing a history of conception exposure can be challenging. 'Contraception' may mean the use of the oral contraceptive pill only, and the duration of trying to conceive may mean only timed intercourse and not time off contraception.

History of the subfertile female includes cycle length, regularity, weight changes and exercise. Dysmenorrhoea, dyschezia, and premenstrual spotting sometimes indicate endometriosis. Relevant history from female relatives should be taken as well as a general and reproductive history. An STI history for both partners is important.

History of the subfertile male includes failed testicular descent, delayed puberty, congenital abnormalities, inguinal hernia repair, torsion and testicular trauma. Viral illnesses are now a rare cause of infertility. Medications, drugs, alcohol and toxins can adversely affect fertility. It can take 4-12 months to recover from testosterone misuse.

Examination

Female examination

Assess overall fitness for pregnancy and review Pap smear status. Evaluate BMI, secondary sexual characteristics and signs of androgenisation. Examine thyroid, breast, abdomen and pelvis. Fibroids or endometriotic nodules in the Pouch of Douglas may be found. Women who decline pelvic examination or who demonstrate vaginismus may need referral for very relevant psychosexual problems.

Male examination

Assess overall health. Male examination is often omitted in preference to semen analysis. Nevertheless, testicular examination is essential with marked oligospermia (less than five million per mL) because there is a 20-fold greater incidence of testicular cancer in these individuals.[4] Palpation should identify the vas deferens, epididymes and any varicoceles. Small testes are associated with diminished sperm production. Signs of hypogonadism may also be present.

Fertility advice

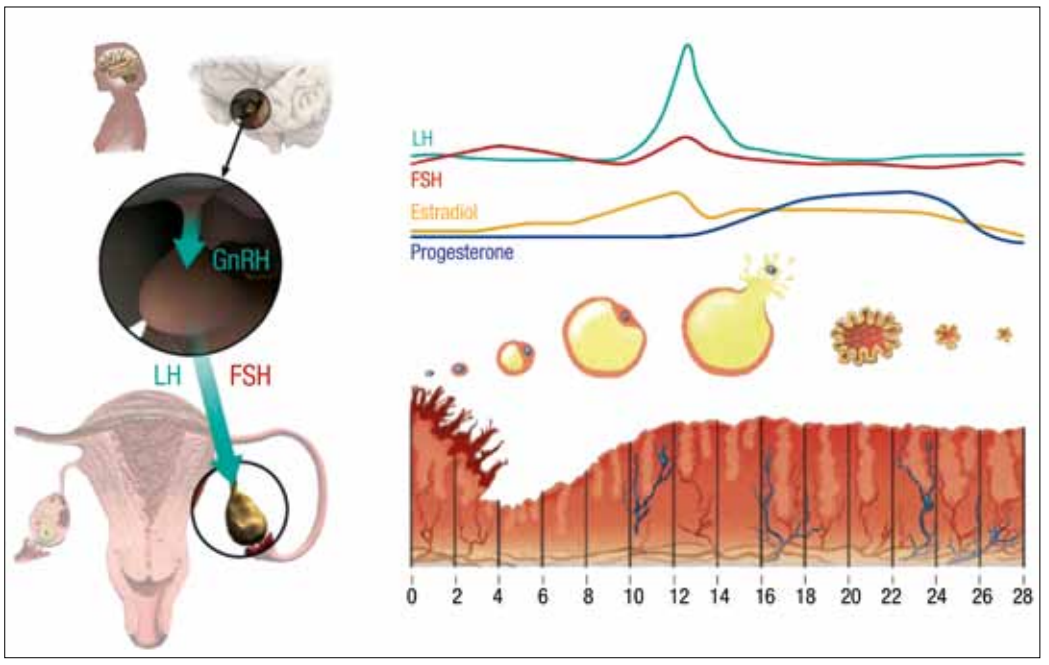
A primary goal is to help the couple understand their fertility and deal with common misconceptions. There is often an unreasonable expectation of immediate pregnancy success. Roughly 90% of couples, where the female partner is under 35, will conceive in the first year off contraception. Of the remaining 10%, about half will conceive the following year.

LH kit manufacturers have encouraged programmed intercourse. Home ovulation analysis can be misleading, however, and the stress of timed intercourse is unhelpful. Abstinence outside the fertile window probably does more harm than good by increasing sperm DNA fragmentation.

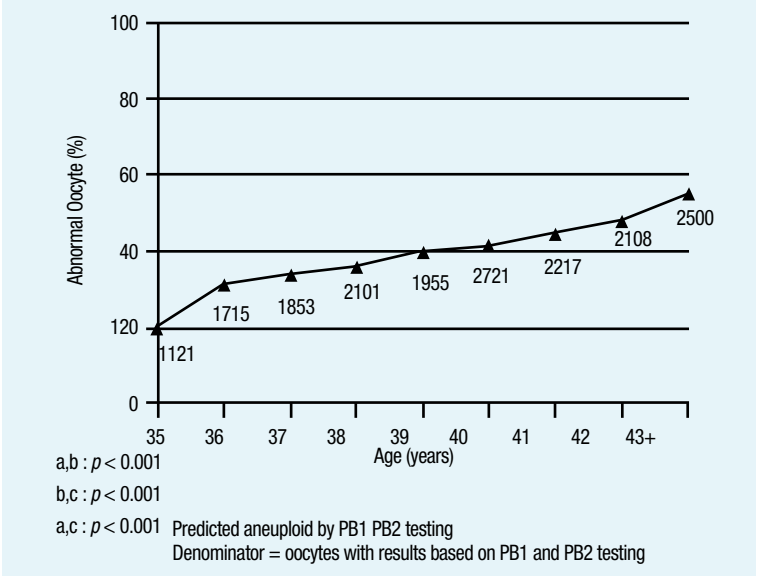
Common clinical challenges include dealing with the impatient couple and, conversely, the couple who are hesitant to progress to appropriate subfertility investigations and management. The anxious or impatient couple are often utilising ovulation analysis and readily want investigation. These couples should be reminded that at best, conception only occurs in 25% of cycles and that premature investigations may raise findings of uncertain significance, leading to therapies of uncertain value.

For women with regular cycles (35 days or less), the fertile window is likely to be 13-19 days ahead of the next period. This allows for the fact that the luteal phase is usually 14 days in length. Conception is most likely in a six-day period, ending on the day of ovulation. Of these six days, the last three have the greatest potential. For women with long and irregular cycles, intercourse at a minimum of two or three times randomly per week is necessary. Intercourse every day or every second day is only slightly more productive. Couples having intercourse less than twice a week may have a degree of 'social' subfertility.

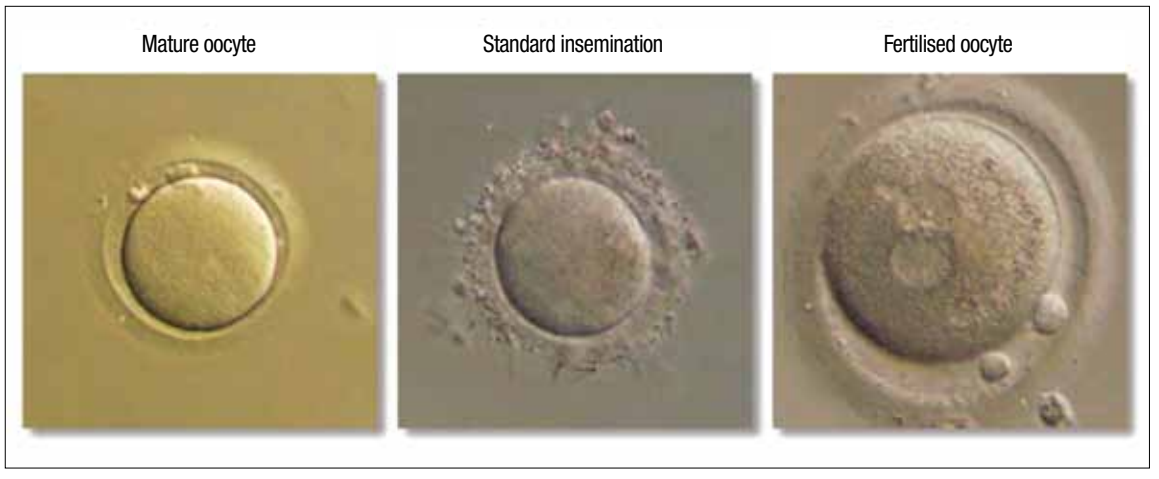
For couples likely to be slow to initiate action, provision of data on declining fertility with age can be a motivating factor. It is vitally important to counsel postnatal women over 35 not to assume another successful pregnancy is a certainty. Recommending a long wait after delivery is poor guidance for older women because a critical window of reproductive opportunity can easily disappear. It may be wise to counsel women with declining ovarian reserve to wean by six months and dispense with contraception thereafter if a second child is highly desired. IVF does not compensate for diminished egg quality.



Menstrual cycle.



Aneuploid oocytes in relation to maternal age. Predicted by PBI and PB2 testing for chromosomes 13, 16, 18, 21 and 22.



In-vitro fertilisation (IVF).

Subfertility investigations

Semen analysis

THIS investigation is always necessary when there is a significant delay in conceiving, but it can cause anxiety. A variety of parameters are measured. These fluctuate over time, and the results are very observer dependent. Minor abnormalities of morphology and motility are common and often of marginal significance. Premature referral of a young couple with good prognosis is therefore not desirable. Follow-up of distinctly poor semen analysis is usually best done through a specialist laboratory because additional parameters may require assessment.

Management should take into account the overall situation. For example, an isolated reduction of normal sperm morphology in the absence of other risk factors, such as advancing age, does not warrant immediate action unless there has been a substantial delay in conceiving. In contrast, a markedly reduced count would warrant immediate measurement of FSH, LH, testosterone and prolactin levels. Other tests likely to be needed are chromosomal studies (karyotyping and testing for Y-chromosome microdeletions), scrotal ultrasound and sperm DNA fragmentation assessment. Azoospermia may necessitate testicle or epididymis access with a fine needle.

Assessment of ovarian reserve

Ovarian reserve evaluation is useful for all women who have been trying to conceive for over a year. For women at high risk of subfertility (eg, those over 35), it is worth considering early testing. Evidence of diminishing reserve necessitates specialist review before the window of therapeutic opportunity is lost.

The easiest test of ovarian reserve is anti-Müllerian hormone (AMH) measurement (pathology

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fee around $85, non-rebatable). AMH is secreted by preantral ovarian follicles and can be ordered randomly despite mild cyclical and seasonal fluctuations. AMH can be a useful predictor of over- or under-response to exogenous FSH and can offer some indication of IVF potential. Measurement of day two or three FSH and oestradiol are not as reliable for assessing ovarian reserve but worth doing if an AMH level cannot be done. These levels can be valuable as follow-up tests. An FSH level ≥10mIU/mL and/or oestradiol levels >200pmol/L on more than one occasion warrants specialist review.

Another method of assessing ovarian reserve is the use of ultrasound to count the more mature antral follicles, although this is operator dependent.

Similar to semen analysis, a test of ovarian reserve simply provides prognostic clues. A low assessment of ovarian reserve does not necessarily correlate with outcome, just as a high assessment should not offer great reassurance when viewed in isolation. As with semen analysis, early testing of AMH or specific ultrasound in low-risk situations can lead to unnecessary anxiety or, worse, an unnecessary cascade of medical activity.

Pelvic ultrasound

Ultrasound can detect gross pelvic pathology but not more subtle conditions, such as endometriosis without cyst formation. An antral follicle count from an expert sonographer is a bonus.

Imaging with contrast media

Hysterosalpingo-contrast-sonography (HyCoSy) ultrasound and X-ray hysterosalpingogram (HSG) can demonstrate tubal patency and some intrauterine pathology. HyCoSy is better for identifying pathology than HSG. Both tests involve some discomfort and a small risk of infection. These tests are sometimes deferred when the short-term conception prognosis is good, quick recourse to IVF is planned or laparoscopy is needed.

Hysteroscopy and laparoscopy

Direct vision remains the gold standard of female infertility investigation, but laparoscopy carries a 1/1000 risk of major injury. IVF is often instigated first in the hope of quick success.

Nevertheless, laparoscopy is particularly worth considering where major pathology is suspected, after IVF failure (some of these women will benefit from identification and resection of endometriosis, present in up to 25%) or when IVF is unlikely to be used.

Sometimes just D&C/hysteroscopy is performed for reassurance regarding embryo transfer and implantation issues.

Management of subfertility

IVF advice

MISUNDERSTANDINGS are prevalent regarding IVF. A simple outline of the process is very helpful if it appears IVF may be needed.

Explaining the IVF process

The key processes take about three weeks. Travel is problematic during this period. Self-administered daily injections usually commence at the start of menses. Ovarian stimulation typically takes 8-11 days with blood tests +/- ultrasound every few days. Employment can continue.

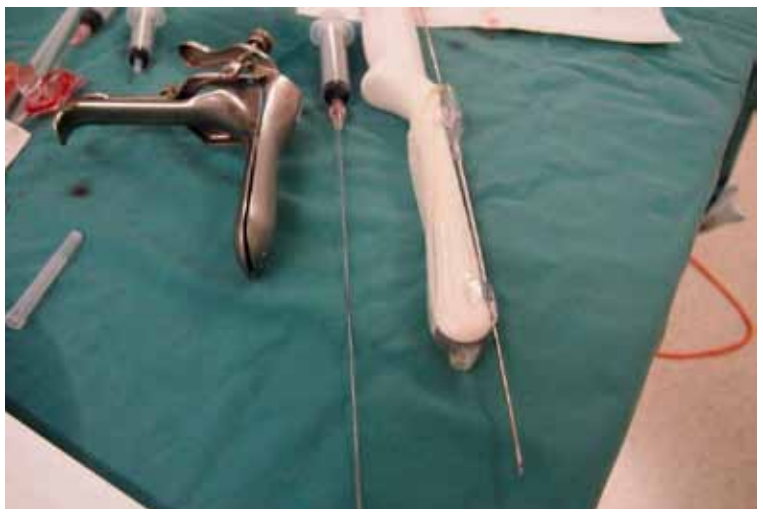
Egg collection is done with a long needle attached to a vaginal ultrasound transducer under local or general anaesthetic. It takes about 15 minutes and is usually well tolerated. This is the only day that must be taken off work. The partner needs to produce a semen sample on this day, but sperm can be frozen in advance. In most cases, there will be an embryo to transfer 3-6 days later using a catheter and speculum. This transfer procedure is little different from a Pap smear from the woman's perspective. A pregnancy test is performed 11 days later. Spare embryos can be frozen. Sometimes, for technical reasons or avoidance of ovarian hyperstimulation syndrome (OHSS), all embryos are frozen. With skilled vitrification, frozen embryos can produce success rates similar to fresh embryos.

The IVF unit

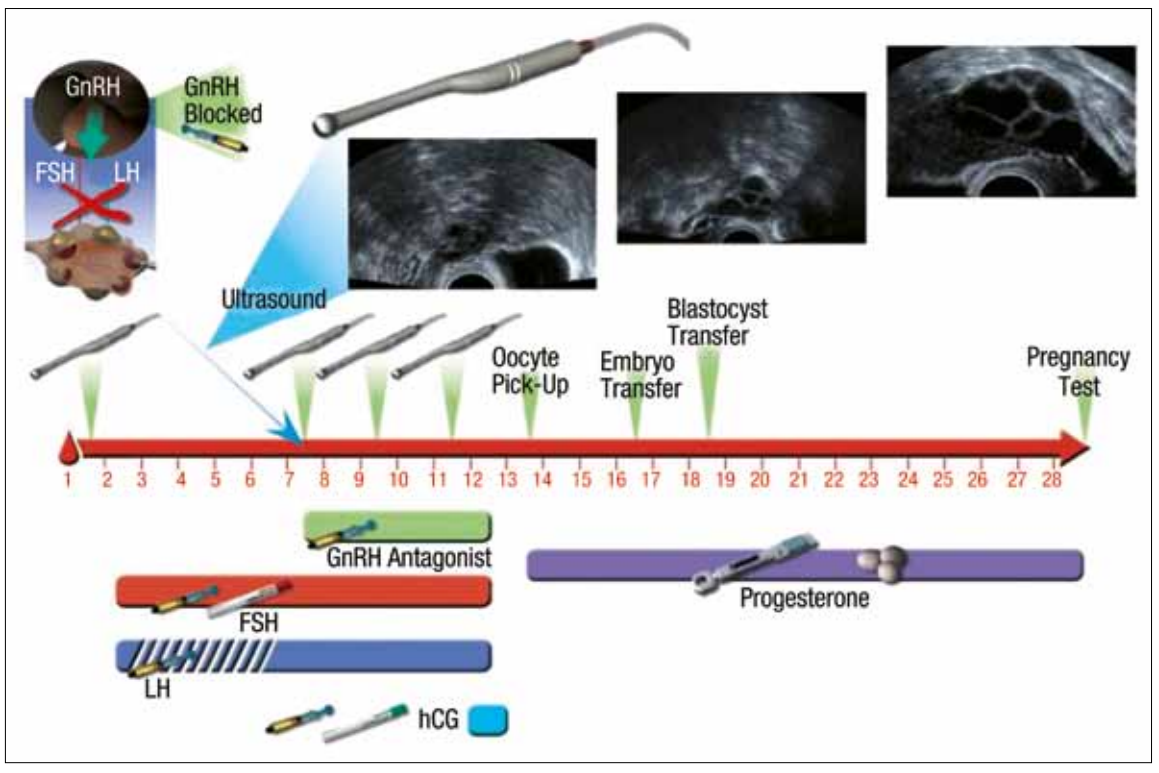
IVF is a team effort dependent on the skills of doctors, scientists, nurses, counsellors and a large administration because the logistics are complex. Commitment to research and development has kept Australia at the forefront of assisted reproduction. The third successful IVF pregnancy, the first frozen-embryo IVF baby in the world and several of the first five ICSI babies were all Australian successes.

Preimplantation genetic diagnosis

Some clinics have the capability of testing embryos for aneuploidy and other genetic defects (preimplantation genetic diagnosis, PGD). This involves taking one to several embryonic trophectoderm cells between days three and six of development and testing them with techniques such as comparative genomic hybridisation. There is, remarkably, minimal embryo loss in this process.



Ooctye collection equipment: ultrasound with guided aspiration needle (the syringe needle is for administration of local anaesthetic).



GnRH Antagonist Protocol.

Single-gene defect analysis can be quick — allowing the possibility of immediate embryo transfer — but more commonly, a complete check is done, which takes days to perform. In the latter case, satisfactory embryos are frozen and transferred at a later date.

PGD has two main uses. The first is to identify embryos carrying specific inherited disorders. The second allows euploid embryos to be selected for transfer — useful given the high rates of chromosomal abnormalities in all early embryos. This is particularly helpful if either partner possesses a chromosomal translocation, in some cases of recurrent miscarriage, and following IVF failure with untested embryos. An embryo shown to be euploid by PGD can offer a 40-80% chance of pregnancy depending on female age. Women over 38, with a high rate of aneuploid embryos, can benefit from PGD, provided a sufficient number of embryos are created to make the selection process worthwhile.

Management of common female subfertility conditions

The following is a consideration of management of some common clinical conditions with respect to IVF and alternatives.

Ovulation disorders

There are three WHO groups of ovulatory disorders: group 1, hypothalamic or pituitary amenorrhoea; group 2, chronic anovulation (mainly PCOS), representing 90% of ovulation disorders; and group 3, failing ovaries with persistently elevated day two or three FSH levels.

Women with a regular 25-35-day cycle are almost certainly ovulating, but a short cycle sometimes indicates declining ovarian reserve. Luteal-phase progesterone levels can be done, but abnormal levels often represent mistiming of the test in relation to ovulation. Remember hyperprolactinaemia and thyroid dysfunction as causes of amenorrhoea.

Group 1 women typically have normal or low day two FSH levels and a thin endometrium due to low oestradiol levels. Clomiphene is usually ineffective. FSH plus LH alone or IVF are options. Fat to muscle ratio is important.

Group 2 women often have PCOS. This diagnosis rests on the patient having at least two of the following features: hyperandrogenism (clinical or raised free-androgen index), oligo- or amenorrhoea, and ovaries of polycystic appearance on ultrasound. It is essential to exclude other causes of hyperandrogenism when there is marked hirsutism or acne, such as late-onset congenital adrenal hyperplasia. The high AMH level often seen in PCOS should not give security regarding age and fertility. All eggs age.

Beyond addressing raised BMI or glucose intolerance, clomiphene (or an aromatase inhibitor) is usually the first step. This carries about an 8% chance of multiple pregnancy. Clomiphene-resistant women will need either ovulation induction with FSH or IVF. FSH carries the advantage of reduced cost, but there is a higher multiple-pregnancy rate (20% per cycle in some studies), and it still entails cycle monitoring with regular ultrasound and hormone assessments. IVF has a much lower multiple-pregnancy rate with a higher probability of success, but it is a more elaborate and expensive process. Women with PCOS are prone to respond exuberantly to FSH, and the superovulation of IVF places them at greater risk of OHSS compared with their peers.

Clomiphene and FSH are unlikely to help women with failing ovaries (group 3). Sometimes donor-egg IVF is the only option. Most IVF doctors will not transfer embryos to women beyond the age of 50.

Tubal disease

Apart from reversing tubal ligation, surgery for damaged fallopian tubes usually fails and carries a significant risk of ectopic pregnancy. IVF is usually the best option in this situation. Hydrosalpinges, as reservoirs of toxic secretions, lower IVF success rates. Ideally, they should be clipped or removed.

Endometriosis

Endometriosis is a frequent finding at laparoscopy for women with subfertility, even among the asymptomatic group. Laparoscopic treatment of moderate and severe endometriosis is likely to improve fertility. The impact of treating minor endometriosis is less certain but probably beneficial. IVF successes can be achieved even when endometriomas are noted during the cycle, but it is generally desirable to perform IVF when the chance of extensive, active endometriosis is deemed low.

Fibroids

Fibroids are common but only occasionally cause subfertility, and myomectomy carries a risk of uterine compromise. Fibroids likely to warrant removal are those that distort the uterine cavity and some large intramural fibroids. Interestingly, fibroid size does not correlate well with fertility outcomes.

Other uterine disorders

Endometrial polyps have an uncertain impact but are usually removed. Other uterine pathology is uncommon. There is usually a bias to avoid surgery if the endometrial cavity has a reasonable capacity with a smooth contour.

Management of common male subfertility conditions

ICSI has become the standard management of male factor infertility. A single sperm is directly injected into the oocyte. It is remarkably effective even with extreme oligospermia and in the absence of any normal morphology. This is because spermatozoa are like cars in that the important component is the driver (sperm head DNA). The car can be a wreck, but as long as the driver reaches the destination, all is well.

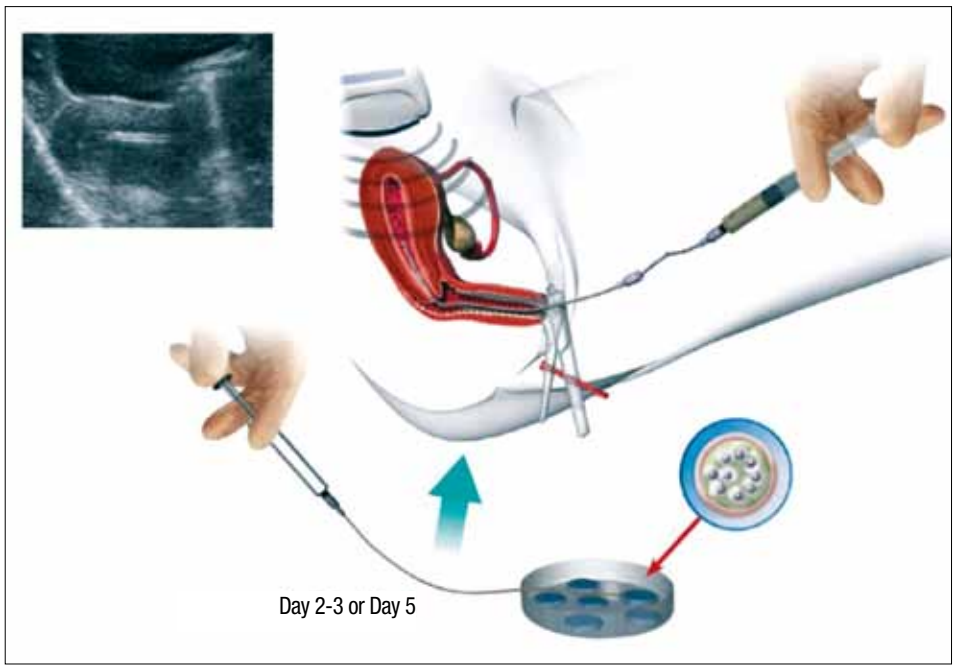
About 3% of all infants are diagnosed with a congenital anomaly (either minor or major). Observed odds ratio for any congenital abnormality is about 1.42 for IVF and 1.69 for ICSI.[7] The raised risks may reflect underlying paternal genetic issues rather than the procedure. Therefore, IVF is preferred to ICSI in equivocal situations. ICSI is essential for PGD, however, as there is a risk of genetic contamination with regular IVF.

Intrauterine insemination (IUI), where semen is prepared and transferred directly into the uterine cavity, can be done as an isolated exercise or in conjunction with ovulation induction (FSH or clomiphene). It may be useful for mild male factor subfertility, unexplained subfertility and as a gentle introduction to more sophisticated technologies. It offers, perhaps, a 5% addition to the natural chance of conception per cycle. Ovulation tracking is needed, and this strategy still entails a significant effort; therefore, many couples opt to proceed directly to IVF/ICSI.

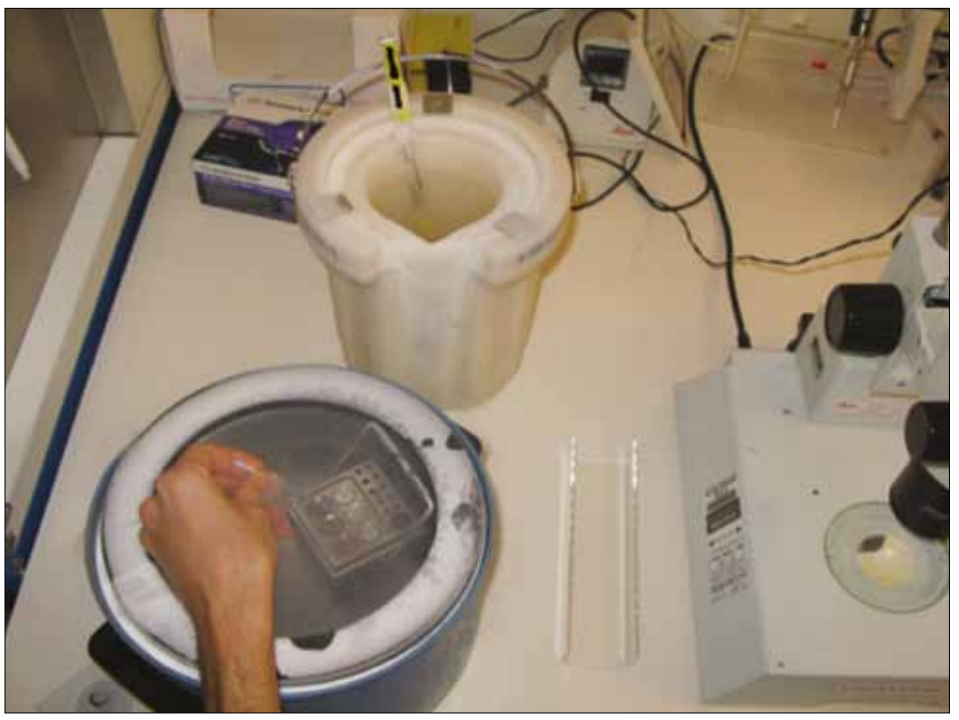
The ultimate measure of success is a pregnancy, as semen analysis is a poorly reproducible test. Studies of varicocele ligation, for example, sometimes show improved semen analysis parameters but no significant increase in the rate of conception. Finally, in azoospermia and extreme oligospermia, sperm can often be retrieved by passing a fine needle into the epididymis or testicle.

Combined-cause, and unexplained, subfertility

The absence of a clear cause is common. Treatment modalities can be considered in order of complexity: clomiphene does not improve fertility in the presence of a regular cycle and does not compensate for declining ovarian reserve. IUI with FSH ovarian stimulation may offer some improvement over natural intercourse, but this is a complex process involving many of the steps of the far more effective option of IVF. IVF typically offers four times the chance of success per cycle over this intermediate measure. A recent study of women aged 38-42 with unexplained failure to conceive showed IVF to be more effective than ovulation induction/IUI in terms of clinical outcome and cost per pregnancy.[5] It is worth noting that, in the absence of other risk factors, the natural chance of conception over 43 years of age approaches the chance with own-egg IVF (ie, both are low-odd events).



Ultrasound guided embryo transfer.



Embryo vitrification. To maximize survival, the embryos are partially dehydrated then snap frozen in liquid nitrogen.

Support

General support

An important predictor of IVF success is the capacity of the couple to undertake a sufficient number of cycles. In a prospective Swedish study, couples were offered three complete IVF cycles at no patient cost. It was estimated that 64% of couples did not achieve a live birth because they did not avail themselves of the full treatment program.[6] Psychological burden is cited as the most common reason for dropout.[8] Keeping couples off the roller-coaster of excessive optimism or pessimism is critical. A good IVF unit will have sufficient staff to provide excellent patient support, with easy lines of communication to small consistent teams. Consistent care from just one specialist has also been shown to lower the rate of premature dropout.

Managing irregular and disappointing treatment cycles

Couples can be counselled that every cycle is unique because each gamete is unique and that the cohort will vary each cycle. Outcome is more likely to be a function of intrinsic embryo quality than of any nuances of stimulation regime. Nevertheless, skilled doctors and scientists will optimise the chance of success, particularly among the difficult cases — many of which cannot be flagged in advance.

IVF side effects and safety

IVF has a very low complication rate and is safer than the pregnancies being sought. There are two main risks, however: OHSS and rare surgical complications, from egg pick-up. The former will be addressed in Part II: Pregnancy after IVF success.

Infection, visceral injury, haemorrhage, and adnexal torsion are all possible but very uncommon. This is not to say that pelvic disease and anatomical variations (eg, overlying bowel) cannot sometimes make egg collection very challenging.

A depth of gynaecological experience is invaluable in these situations.

Cancer rates do not appear to be increased among women who have undertaken IVF. The slightly raised risk of congenital abnormalities may be a consequence of IVF or an inherent function of subfertility per se.

This will also be considered in more detail in Part II: Pregnancy after IVF success.

Case study

ALANA F, 39, attends alone for fertility advice. She is nulligravid and generally well. She has a regular 26-day cycle and has not used any contraception for the past nine months. Her 50-year-old partner, Sam T, has two children from his first marriage and is uninterested in fertility management.

Further history and examination are unremarkable. Routine pre-pregnancy advice is given. Folate is in use. Rubella immunity is current.

It is reasonable to order basic tests considering Alana's age. An AMH level, pelvic ultrasound — including HyCoSy for tubal patency — and semen analysis are arranged. Alana F is provided with information regarding the diminishing window of opportunity to conceive (both with and without IVF) for women in their late 30s. This may be particularly beneficial for her partner.

Alana F returns two months later to discuss test results. The ultrasound was normal, and tubal patency was demonstrated. A semen analysis has not yet been

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Declaration of interest statement

The author holds shares in Genea.

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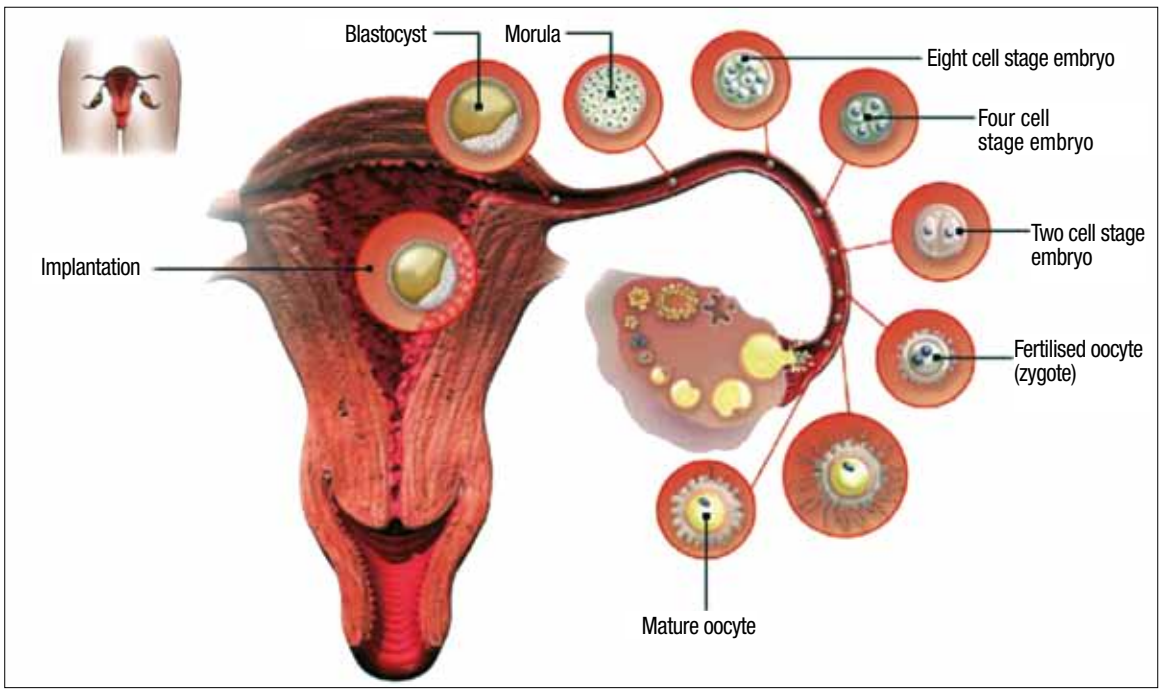
done. Alana's AMH level is 3pM, and her antral follicle count is 4. Both indicate low ovarian reserve in absolute and relative terms.

Like a 'sliding door' sequence of events, there are three common scenarios in this situation: a) the couple proceed to IVF (Australian live delivery rate per embryo transfer cycle for this age group is 22.6%) and probably achieve a baby either through this or naturally, b) they do not do IVF and have a baby naturally or c) unfortunately all too often the following scenario occurs:

Alana F presents again at 42 years of age (Australian live delivery rate per embryo transfer has now reduced to 8.8% for women aged 40-44) with a now-sympathetic Sam T in attendance. He undergoes a semen analysis, which shows reduced motility of uncertain significance. They proceed to IVF and fail all three cycles attempted. They return again when Alana F is 45 to discuss the possibility of travelling to the US for donor eggs or having donor eggs shipped to Australia from an international egg bank. However the couple eventually decides not to proceed with this.



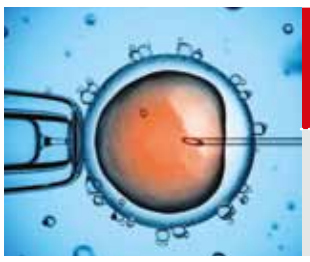
Embryo development and implantation.

Conclusion

SUBFERTILITY encompasses a great variety of situations and is not a progressive disease. Management strategies hinge on female age, aetiology, access to services and, particularly, the attitude of the couple. It is therefore very important to encourage a realistic appraisal of each situation to reduce the likelihood of the common problems of investigation and management being initiated too soon or too late. IVF often represents an effective solution. It is a tragedy to meet an earnest couple with long-standing subfertility who resort to IVF only when the probability of IVF success has greatly diminished as a result of increased female age. If all women over 35 presented for review after six months without contraception, the 'too late' scenarios would be reduced.

Summary

- Subfertility is as much a prognosis as a diagnosis.
- Time and female age are critical considerations. Success rates decline from the mid-30s onwards. This decline accelerates from 38 years of age. Assessment of women over 35, after six months of trying to conceive, is recommended.
- A key challenge is to keep couples on a steady course while undergoing IVF. It can be a rollercoaster of extreme pessimism and extreme optimism. The law of probability needs a chance.
- Following success, a timely return to IVF is essential for older subfertile couples.



How to Treat Quiz

Part I — Subfertility and IVF — 20 March 2015

INSTRUCTIONS

Complete this quiz online and fill in the GP evaluation form to earn 2 CPD or PDP points.
We no longer accept quizzes by post or fax.

The mark required to obtain points is 80%. Please note that some questions have more than one correct answer.

GO ONLINE TO COMPLETE THE QUIZ

www.australiandoctor.com.au/education/how-to-treat

1. Which TWO statements regarding normal fertility are correct?
a) Oocytes are present since mid-fetal life while men make spermatozoa on a seven-day cycle.
b) Through complex feedback loops, involving FSH from the pituitary and oestrogen from follicles, usually only one follicle will reach ovulation.
c) The post-ovulation follicle becomes the corpus luteum and secretes progesterone, preparing the endometrium for implantation.
d) Spermatozoa survive in the genital tract for up to 14 days, with good fertilisation potential in the first 2-3 days.

2. Which THREE statements regarding the physiology of IVF are correct?
a) The aim of IVF is to mature a number of ovulatory follicles by interfering with the mechanism that normally leads to just one dominant ovulatory follicle.
b) Under the influence of FSH and a secondary medication, a whole group of follicles is allowed to mature.
c) Eggs are collected transabdominally from large preovulatory follicles by ultrasound-guided aspiration and are placed with prepared spermatozoa to allow for 'natural fertilisation' in standard IVF (not ICSI).
d) Following embryo culture and support of the endometrium with human chorionic gonadotropin or progesterone, an embryo is transferred to the uterus via the cervix.

3. Aside from female age, which of the following THREE groups commonly cause subfertility?
a) Ovarian dysfunction
b) Uterine dysfunction
c) Male factor
d) Unexplained

4. Which THREE statements regarding infertility in men are correct?
a) Small testes are associated with diminished sperm production.
b) Men with marked oligospermia have an increased incidence of testicular cancer.
c) Viral illnesses commonly cause infertility.
d) Sperm counts can take up to four months to recover after testosterone abuse associated with the gym.

5. Which THREE statements regarding general health in subfertile couples are correct?
a) Supplement with folate
b) IVF success rates are substantially reduced for women with abnormally raised BMIs.
c) Smoking does not impact on fertility.
d) There is little evidence to support the use of complementary therapies aimed at enhancing fertility.

6. Which TWO statements are correct?
a) A semen analysis should be performed in all men when there is anxiety regarding failure to conceive.
b) A semen analysis is always necessary when there is a significant delay in conceiving.
c) The most useful test of ovarian reserve is FSH level, measured at two different points in the monthly cycle.
d) Ovarian reserve may also be assessed using ultrasound to count the more mature antral follicles.

7. Which TWO statements are correct?
a) Ultrasound is a first-line test to identify gross pelvic pathology.
b) X-ray hysterosalpingogram (HSG) is a better overall test for identifying pelvic disorders than hysterosalpingo-contrast-sonography (HyCoSy).
c) Laparoscopy is a very safe procedure, with serious bowel and vascular injuries occurring at a rate of one in 10,000.
d) Sometimes just D&C/hysteroscopy is performed for reassurance regarding embryo transfer and implantation issues.

8. Which TWO statements are correct?
a) The key IVF processes take about three weeks.
b) Ovarian stimulation usually takes eight to 11 days.
c) Egg collection is always done under general anaesthetic.
d) Egg collection is complex and laborious and may take several hours.

9. Which TWO statements are correct?
a) About 90% of couples, where the female partner is under 35, will conceive in the first year off contraception.
b) The kits and apps that advocate the precise timing of intercourse are invaluable in assisting subfertile couples to conceive by indicating intercourse schedules.
c) For women with regular cycles (35 days or less), the fertile window is likely to be 13-19 days ahead of the next period.
d) Women aged over 35 who have successfully delivered a child conceived through IVF have an excellent chance of a second IVF pregnancy.

10. Which THREE statements are correct?
a) Spontaneous conception rates in women aged in their 20s are about 25% per cycle.
b) Men and women's fertility declines equally with advancing age.
c) There are wide differences between Australian clinics (eg, the live-birth rate of fresh cycles for women under 35 in 2012 in different units ranged from 5.4% to 38.6%).
d) An estimation of the probability of conception in the ensuing 12 months will dictate overall strategy.

CPD QUIZ UPDATE

The RACGP requires that a brief GP evaluation form be completed with every quiz to obtain category 2 CPD or PDP points for the 2014-16 triennium. You can complete this online along with the quiz at **www.australiandoctor.com.au.** Because this is a requirement, we are no longer able to accept the quiz by post or fax. However, we have included the quiz questions here for those who like to prepare the answers before completing the quiz online.

Australian Doctor Education

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NEXT WEEK

Early pregnancy failure is common following IVF conception. Once pregnancy has been achieved through IVF, a specific regimen is followed to ensure optimum maternal and fetal health. This includes hormonal support, pathology, pre-implantation genetic diagnosis, ultrasound, planning for delivery as well as planning for any proposed future IVF conceptions. The author is **Dr David Shelley-Jones**, accredited specialist, Genea and VMO obstetrician and gynaecologist, Mater Hospital, North Sydney, NSW.