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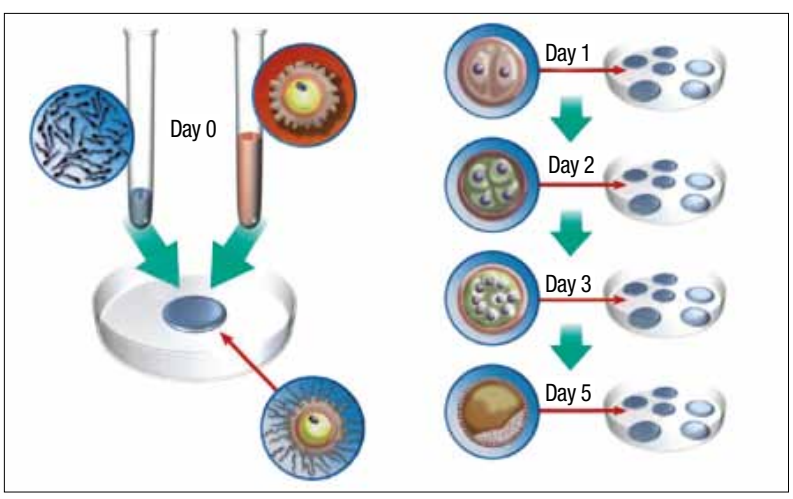
Part II – PREGNANCY AFTER IVF SUCCESS

Introduction

A BILLBOARD promoting medical research advised that the first few weeks of life are the most dangerous. Someone had written underneath, "… and the last few weeks are pretty dodgy too". Beyond the exciting moment of receiving news of a positive pregnancy test, the IVF couple — having already been on a challenging road — now face further uncertainty.

IVF pregnancies require delicate handling for two reasons. Early pregnancy failure, which is not uncommon, may offer even greater suffering than usual, given the effort to achieve success and the sometimes poor prospects for achieving another pregnancy. Second, IVF pregnancies have statistical variance from other pregnancies on a number of measures. These variances may be secondary to the nature of the IVF population or as a result of the IVF process. It is believed the former offers most of the explanations but study is ongoing. Irrespective of academic considerations, knowledge of what an IVF pregnancy implies is of great practical value, as about 3.8% of all babies born in Australia are now the result of this technology. Reassuringly, IVF babies are not deemed to routinely need follow-up, and the method of conception becomes very much a background issue when a healthy child is playing in a park.



In-vitro fertilisation (IVF).

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INSIDE

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Early pregnancy (0-7 weeks)

Confirmation and monitoring

FROM 30-60% of early human conceptions are aneuploid and destined to fail (usually very quickly). The first beta-human chorionic gonadotropin (beta-hCG) level, performed 11 days after embryo transfer (ET), can provide some clues as to viability. A level greater than 100 IU/L is very encouraging. A level of less than 50 is discouraging. A beta-hCG rise of more than 66% over 48 hours is suggestive of viability, although the chance of miscarriage or ectopic gestation is not entirely eliminated.

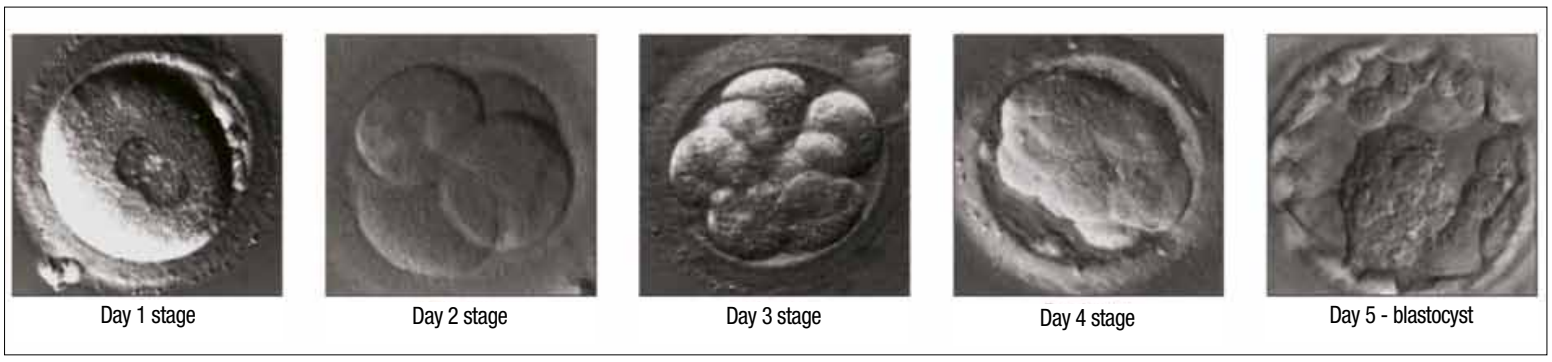
An ultrasound is usually done at seven weeks. Ectopic pregnancy (incidence of 1.3% in IVF gestations) must not be forgotten. A correctly placed embryo can drift. It is particularly important to ensure poor beta-hCG levels are tracked to less than 5 IU/L because chronic ectopic pregnancies can be found with low-level beta-hCGs.

Miscarriages occur at the same age-related rates as naturally conceived pregnancies. Management can follow usual protocols, although there is often a bias to curettage unless it is a very early loss. Karyotyping products of conception, particularly when there has been a history of failed IVF or miscarriages, can be useful when planning further management. If, for example, the lost pregnancy was shown to be aneuploid, the case for a planned investigative laparoscopy (or other surgical procedures) is diminished. Further, older women, with declining egg quality/reserve, are often keen to proceed quickly to further IVF and are unwilling to wait the several months it may take for natural resolution of miscarriage.

Hormonal support

The IVF doctor and clinic nurses will monitor a pregnancy at least through to the viability ultrasound. Particular focus is placed on ensuring sufficient progesterone to nurture an early pregnancy. There are three main categories of IVF pregnancies in this respect: those arising from stimulated cycles, those from programmed (medicated) frozen cycles and those from natural frozen cycles. In programmed frozen cycles, there is no ovulation and therefore no corpus luteum formation. Progesterone (usually pessaries) is therefore required until at least 10-11 weeks' gestation when placental production is adequate.

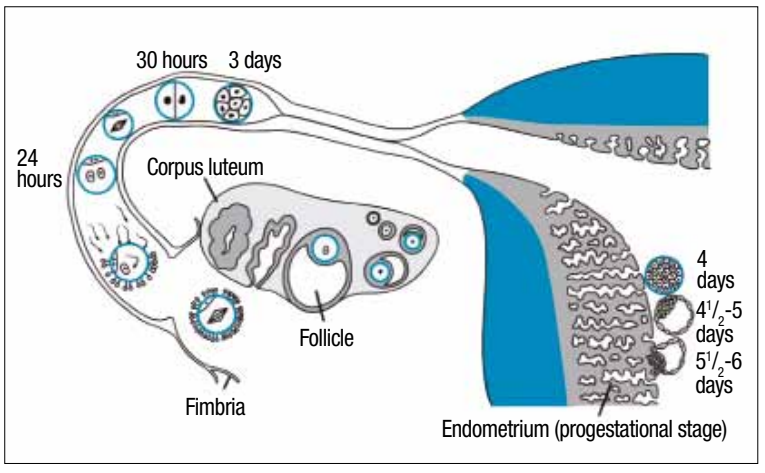
In stimulated cycles, high levels of oestrogen and progesterone suppress luteinising hormone (LH) secretion, leading to early luteolysis. Natural cycles, relying on ovulation and corpus luteum formation, do not routinely need ongoing supplementation, but progesterone levels are carefully assessed.



Embryo development.

Table 1: Classification of OHSS

OHSS may be early onset (within nine days of hCG trigger) or late onset (more than nine days post–hCG trigger) with severity indicated below.
Mild OHSS
Abdominal bloating
Mild abdominal pain
Ovarian size usually less than 8cm*
Moderate OHSS
Moderate abdominal pain
Nausea ± vomiting
Ultrasound evidence of ascites
Ovarian size usually 8-12cm*
Severe OHSS
Clinical ascites (occasionally hydrothorax)
Oliguria
Haemoconcentration, haematocrit greater than 45%
Hypoproteinemia
Ovarian size usually greater than 12cm
Critical OHSS
Tense ascites or large hydrothorax
Haematocrit greater than 55%
White cell count greater than 25,000mL-1
Oliguria/anuria
Thromboembolism
Adult respiratory distress syndrome (ARDS)
*Ovarian size may not correlate with severity of OHSS in cases of assisted reproduction because of the effect of follicular aspiration.
Source: Prakash A and Mathur R. Ovarian hyperstimulation syndrome. *The Obstetrician & Gynaecologist* 2013; 15(1):31-53.



Fertilisation and embryo development in nature.

Ovarian hyperstimulation syndrome

Ovarian hyperstimulation syndrome (OHSS) is a widely recognised complication of ovarian stimulation for IVF or ovulation induction (OI). The incidence is fortunately decreasing through improved drug regimens and other management strategies, such as freezing all embryos collected when the risk seems great. The condition remains incompletely understood. It ranges in degree from mild (3-4% of cycles) to severe (potentially life-threatening in 0.1-0.2% of cycles) (see table 1). Women with PCOS have a raised risk because they tend to have idiosyncratic responses to FSH.

Mild abdominal distension is common just ahead of egg collection. Women with OHSS develop worsening symptoms typically 3-5 days after egg collection, and there is marked deterioration in the event of conception.

A haematocrit greater than 0.44 is of particular concern. Management of fluid intake is important because it is easy to cause dangerous fluid overload. A thromboembolic event is the most dangerous risk among women with markedly raised oestrogen levels but fortunately rare. It should be noted that if the woman has not conceived, the condition is generally self-limiting and resolves spontaneously. The worst of OHSS is usually over by seven weeks' gestation.

Multiple pregnancy

In recent years, most IVF cycles in Australia have involved single-embryo transfer (SET). Despite the appeal of an immediate family of four to a couple struggling to conceive, multiple pregnancies are problematic. Twins represent eight times the risk of cerebral palsy, and this incidence is dramatically increased in triplets (47 times the risk).[2]

There are two common mechanisms for a twin IVF pregnancy and one rare potential mechanism. Obviously, transfer of more than one embryo increases the chance of dizygotic twinning. Double-embryo transfer (DET) has declined in Australia over the past few years, and the splitting of a single embryo, monozygotic twinning, is accounting for an increasing proportion of IVF twins. If the proscription of intercourse during a stimulated cycle is ignored, there is also the potential for a third mechanism: 'untapped' follicles can ovulate and be fertilised.

The assisted reproduction technology (ART) twin rate reached a peak of 21% in Australia in 2001. This declined to 8.4% in 2008 and 6.6% in 2012.[1] Of these twin deliveries in 2012, three-quarters arose from DET and one-quarter were monozygotic: the decline largely a result of the trend to SET. By comparison, the proportion of multiple deliveries in Australia from all conceptions in 2011 was 1.5%.[3] The trend to SET has, counter intuitively, not come at a cost of decreased success rates per stimulated cycle. This decrease in the multiple delivery rate was achieved while clinical pregnancy rates remained stable at around 23% per initiated cycle. Elective SET results in a higher chance of delivering a term singleton live birth compared with DET. Although this strategy yields a lower pregnancy rate than a fresh cycle DET, the difference is almost completely overcome by an additional frozen SET.[4] Improved freezing technology (vitrification) means embryos can be used in subsequent cycles, and there is even some evidence that the less-stimulated endometrium of frozen cycles (usually no FSH used) is more receptive.

Most of the cases of DET are confined to situations where embryo quality appears poor — but even in these cases, multiple pregnancies arise. Fortunately, triple-embryo transfer is now considered extremely poor practice in many countries and is rarely seen. Triplet deliveries are a rare event in Australia for both natural and IVF conceptions.

Liaising with the IVF clinic

Open lines of communication among the IVF doctor and clinic nurses, GP, and patients are of utmost importance in the early period where there is the potential for suboptimal care relating to uncertain clinical responsibilities. Well-resourced clinics mitigate this risk by providing 24-hour helplines with access to specialist doctors.

Travel

As IVF and pregnancy are two independent risk factors for rare but potentially life-threatening thromboembolic events, it is a good idea not to add a third risk factor: long-haul air travel. Further, remote travel before a viable intrauterine pregnancy is confirmed is an unnecessary risk.

8-12 weeks

Booking visit

THE initial obstetric visit after a satisfactory viability scan largely proceeds along the usual lines. Routine tests, some of which will have recently been done, include FBC, blood group and antibody screen, rubella antibody status, syphilis serology (specific Treponema pallidum assay), MSU (biochemical analysis and culture), HIV, hepatitis B serology, hepatitis C serology, varicella, and cervical cytology (if a cervical Pap smear would fall during the pregnancy). Additional tests that may be considered are screening for haemoglobinopathies, vitamin D, CMV and TSH.

Folate 400mg (or more) daily is ideally already being taken, and some authorities recommend iodine 150mcg daily. Routine screening for vitamin D deficiency and/or routine supplementation is not a current recommendation. Aspirin and calcium are sometimes used as pre-eclampsia prophylaxis on an individual — but not a population — basis. Iron supplementation is not needed on a routine basis.

It is usually easier to provide the government dietary guide (readily available) than spend an exorbitant amount of time speculating about individual items of food. The subject of food can cause anxiety, even though cases of congenital listeria and toxoplasmosis

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are very uncommon. Encouraging a high-fibre, low-GI diet is likely to have benefits in curtailing the problem of relatively large babies in affluent societies. Exercise in moderation is reasonable, with the proviso that the ovaries are quite enlarged for many weeks following a stimulated cycle. It is a good idea to encourage the couple to fully postpone celebrating their success until the 12-week scan is performed. IVF pregnancies can be emotionally charged, and there is still a significant risk of losing any pregnancy between 7-12 weeks' gestation.

Screening before the 12-week ultrasound

Preimplantation genetic diagnosis and non-invasive prenatal test

IVF doctors, given their 'active' involvement in conception, are usually keen to mitigate the risk of heritable disease — particularly as preimplantation genetic diagnosis (PGD), in which a few cells are taken from the embryo for testing, can be done in some of the larger IVF clinics.

A single blood test can identify the carrier status of prospective parents for certain conditions (eg, cystic fibrosis, which is recessive, with a one in 2500 incidence in the Caucasian population), and there are now 'panel' tests for a large number of hereditable diseases. Couples at risk can then be counselled regarding their options before embarking on IVF and may opt to use only embryos that have been shown to be unaffected through PGD. This panel testing has the potential to reduce the incidence of some serious conditions.

Biopsied trophectoderm ready to be tested via PGD.

PGD – PCR analysis. Cell transfer and genome amplification. The cells biopsied from the embryo are washed and transferred into a reaction tube.

If IVF success involves PGD selection, there will usually be a general evaluation for common aneuploidies, such as trisomy 21. Routine screening for Down syndrome is still recommended, however, as there is a very small chance of the condition being missed through DNA contamination.

There is also a new maternal blood test, the non-invasive prenatal test (NIPT), for Down syndrome screening that can be done from 10 weeks' gestation onwards. It involves identifying and testing cell-free DNA within the maternal circulation (≥99.5% sensitivity, ≥99.8% specificity for Down syndrome). Costing between $400 and $750 (no rebates), it can be organised through most pathology services, obstetric ultrasound practices and some IVF units.

This test can be offered to all couples, but it will be of most value to women at high risk of Down syndrome (eg, over 38 years old, no PGD) who wish to know their status in this regard as soon as possible.

Many couples, however, prefer to review this option after the 12-week screening ultrasound (nuchal translucency) and associated serology, given the expense. At this point, this new test is invaluable as a safe, non-invasive way of further assessing those with an intermediate risk estimate.

If Down syndrome (or another aneuploidy) is detected, diagnostic confirmation with chorionic villus sampling (CVS) or amniocentesis is still required because of the residual chance of error.

The 12-week ultrasound and serology

An ultrasound (11-13 weeks) is worth doing for all IVF couples if only to ensure pregnancy progression and, likely normal, morphology. Late diagnosis of major problems adds considerable distress, as there is usually much celebration for these hard-won pregnancies.

The addition of fetal assessment for Down syndrome will pick up 75-80% of these cases (and some other aneuploidies as well), but if serology is used in conjunction with ultrasound assessment, the sensitivity rises to 85-90%.

Further, the associated serology has additional value; for example, low pregnancy-associated plasma protein (PAPP) serum levels can prompt extra surveillance for later fetal growth restriction (FGR).[5]

It is worth remembering that in the case of donor-egg IVF, the chance of Down syndrome is largely related to the age of the egg donor — this person is usually much younger.

Arrangement for a visit at 14 weeks' gestation is helpful in ensuring all the early phase tests and screening processes have been reviewed.

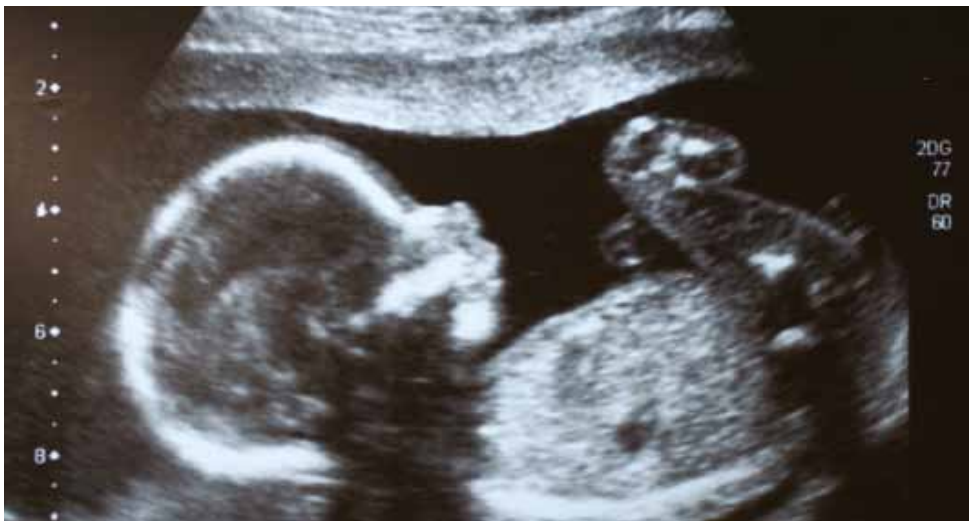
Second trimester

THIS is the safest trimester, and generally, care is routine, including a review of any screening tests and a 19-week morphology ultrasound. Further blood tests are performed at 26-28 weeks, including an FBC, blood group antibodies (if Rh negative) and screening for gestational diabetes. Risk of the latter is increased in the IVF population secondary to an increased average maternal age.

While iron supplementation is not routine, it is often worthwhile, particularly if the haemoglobin level at 26-28 weeks is suboptimal. Many women who definitively require iron supplementation take random over-the-counter preparations, which can have poor efficacy. Therefore, it is important to be specific when oral iron is needed.

More than 500mL of blood is lost in 10% of deliveries, so a good blood count can be critically important in the event of a major haemorrhage.

The ideal time for long-haul and remote travel is 20-24 weeks, although neither is encouraged at any time. Apart from DVT risks, an altitude of 30,000ft or a remote Pacific island are not good places for an emergency. It is worth pointing out that a baby born at 28 weeks' gestation in Australia has a high chance of survival while its chances are signifcantly lower if delivered in a developing country. If intent on such travel, the couple should be encouraged to check individual airline policy and consider obtaining insurance for the unborn child.



Third trimester

THE majority of mildly increased relative risks in IVF pregnancies beyond 20 weeks reflect intrinsic differences in the IVF population (eg, female and, possibly, male age; pelvic pathology; comorbidities; and, perhaps, factors that have not been elucidated). Each case must be judged on its own merits. For example, a 30-year-old woman in good health with an unremarkable history is not particularly at risk.

The subfertile population in general, irrespective of treatment, is clearly associated with an increased risk of adverse outcomes in pregnancy — a prolonged time to pregnancy is of significance.[6] IVF pregnancies have a mildly increased relative risk of low birth weight (LBW), FGR, preterm birth, and perinatal morbidity and mortality.

Premature labour is more likely following IVF — nearly one in six babies (17%) were preterm (less than 37 weeks' gestation) in 2011, markedly higher than the proportion of preterm babies (8.3%) born in Australia in 2010.[3] FGR is more likely in relative terms but still infrequent in absolute terms (two-fold increase).[7] A study on subfecundity and neonatal outcome from the Danish national birth register found subfecundity per se may be associated with an increased risk of neonatal death.[8]

Table 2: Risk of Down syndrome and other chromosomal abnormalities

Maternal age at delivery	*Chance of having live-born baby with Down syndrome	**Chance of having a live-born baby with a chromosomal abnormality
25 years	One in 1383	One in 476
30 years	One in 959	One in 385
33 years	One in 589	One in 286
36 years	One in 259	One in 149
39 years	One in 113	One in 81
42 years	One in 52	One in 39
45 years	One in 32	One in 19

*Morris JK, et al. Revised estimates of the maternal age specific live birth prevalence of Down's syndrome. *Journal of Medical Screening* 2002; 9:2-6.
**Hook EB. Rates of chromosomal abnormalities at different maternal ages. *Obstetrics & Gynecology* 1981; 58:282-85.

Singleton infants born after IVF are at an increased risk of LBW, with the ovarian stimulation–induced maternal environment appearing to represent an independent contributor to this risk.[9] A recent study found the number of LBW infants was statistically higher in subfertile patients as compared with fertile patients (relative risk = 1.68), and this risk persisted among subfertile patients who used IVF (relative risk = 2.0).[10]

A welfare ultrasound at 34 weeks' gestation, irrespective of clinical findings, can be reassuring for both patient and doctor. Late loss of an IVF pregnancy is devastating, particularly in cases

where the duration of infertility is long with many IVF attempts. This ultrasound can occasionally reveal evidence of fetal jeopardy not identified at routine antenatal visits, especially in cases where obesity makes examination difficult.

Testing in the third trimester also includes repeat blood group antibodies (Rh negative) and an FBC. A vaginal swab for group-B streptococcus is recommended at 35-37 weeks. Hypertension is a little more common in the IVF cohort, often reflecting the increased average age of the mothers to be. It is interesting to note that donor-egg IVF conceptions have a raised risk of pre-eclampsia, possibly the result of altered placentation secondary to the interaction of three genetic lines (donor, mother and father). A recent multicentre case-control study with a cohort of 580 participants showed pre-eclampsia was more than four times higher in women who had received donor

eggs compared with women who used their own eggs.[11]

IVF and older women

The reproductive period has been markedly extended with the use of donor oocytes and fertility preservation techniques, with an increase in the number of women over 40 giving birth for the first time. In 2011, women aged 40 and over made up 4.3% of all women giving birth, compared with 3.0% in 2002.7 According to the Australian Institute of Health and Welfare, 27.4% of donor-egg recipients are 45 or older.

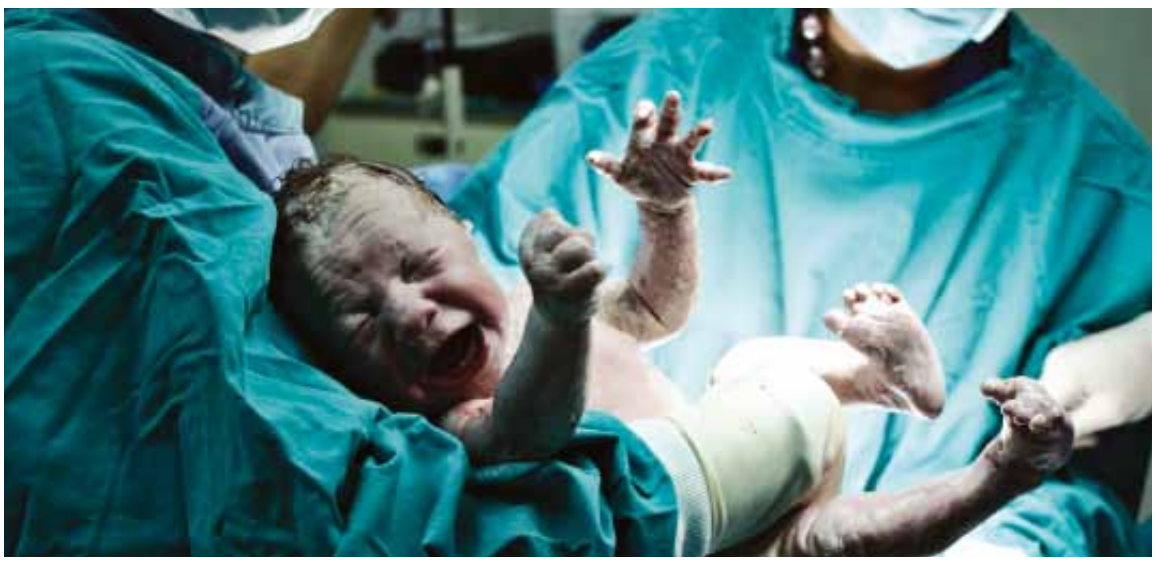
Increasing maternal age is associated with a raised relative risk of adverse pregnancy outcomes, including early miscarriage and Down syndrome (see table 2). Advanced maternal age is associated with a raised risk of fetal loss at any gestation, including during the perinatal period (20% at age 35 vs 54.5% at 42). This is largely driven by early miscarriage — such that after the age of 45, the rate of miscarriage is greater than 50%. The risk of stillbirth at term and beyond in a recent Australian study was one in 1177 ongoing pregnancies for women under 40 but one in 455 for women aged 40 or over.[12]

The risk of LBW and preterm delivery triples in older mothers, and intrapartum complications, such as increased labour times and a greater chance of caesarean and operative delivery, are also raised.[13]

Older women are also more likely to have existing medical disorders (eg, hypertension, cardiovascular disease, diabetes). Hypertension is present in 25% of women 45 and over. This can have effects on fetal growth, the development of superimposed pre-eclampsia, placental abruption and stillbirth, and it triples the risk of perinatal mortality. MI risk is also raised, but the absolute risk remains low. In the uncommon event of life-threatening obstetric complications, women with advanced cardiovascular disease may be unable to adequately compensate. Since severe adverse outcomes of pregnancy — including maternal death, stroke and MI — are rare, it is difficult to ascertain true relative risks from such case series without population data.

Delivery

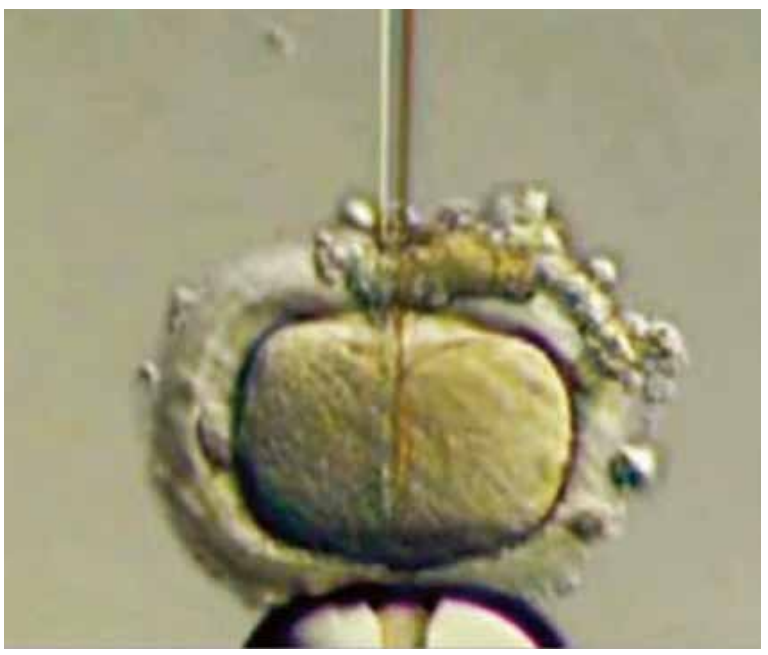
TIMING and mode of delivery are something of a philosophical question for both the doctor and couple. IVF per se is not an indication for any particular delivery strategy but rather the fact that the pregnancy did not come easily and that sometimes, particularly for women with poor egg quality/ovarian reserve, the pregnancy represents the last roll of the dice. There is often understandable enthusiasm to take the prize and go home. Statistics are an important part of the discussion. The chance of stillbirth at 40 weeks and beyond climbs after age 34. The relative risk for nulliparous women between 35 and 39 is 1.42, but this rises to 4.05 (or one in 247 ongoing pregnancies) for nulliparous women aged 40 or over.[12] Inductions in unfavourable conditions (eg, long, closed cervix with a high, unengaged vertex presentation) can create a new set of problems, however. Therefore, each situation needs to be judged on its own merits and discussed in isolation of community pressures. It may be desirable, for example, to wait for natural labour in the case of a 25-year-old woman with blocked tubes while a 40-year-old at term with an unfavourable cervix may elect to be delivered by caesarean section. This would also take into account the higher rate of failed progress in labour for the latter.



Postnatal and long-term issues for mother and baby

Postnatal visit

THERE is one vital element to the consultation post IVF success: fertility planning. It is not at all uncommon to meet couples who have achieved their first child on the first or second embryo transfer but who are struggling to achieve a second successful pregnancy. Often the critical factor is female age. For example, the first conception may have taken place when the woman was 33 (Australian IVF live delivery per initiated cycle is 24.8% in women aged 30-34) while the chance at a current age of 37 is reduced by nearly a third (17%). Individual clinic success rates can vary markedly, but all units record this proportionate reduction. There is also the additional possibility of evolving pelvic pathology (eg, endometriosis and fibroids). It is essential, therefore, to encourage a realistic sense of probabilities during an emotionally labile time, where the ups and downs of euphoria and sleep deprivation can affect judgement. Despite heavy emphasis on this message, it is surprising how often couples at substantial risk of infertility turn up years later for further IVF, expecting another quick success.



Intracytoplasmic sperm injection, also known as ICSI, involves micro-injection of a single oocyte by a single sprem. ICSI and Embryo development.

Frozen embryos do not provide a great deal of future reassurance if they are collected after the age of 35 because the aneuploidy rate will be relatively high. In this case, it is wise is to embark on a further IVF cycle in reasonable time, as a further fresh cycle (ie, collection of 'real-time' eggs) may be needed. Good advice for women over 35, if another child is desired, is to consider weaning at six months and to contact the IVF doctor at this point. Any breastfeeding within two months of an IVF procedure may reduce its chance of success. Of course, where there is absolutely no intention ever to undergo another egg collection, there is less time pressure (as frozen embryos will not age).

It is surprising how often couples at substantial risk of infertility turn up years later for further IVF, expecting another quick success.

For those who do not wish to conceive again, all the usual contraceptive options can be entertained. It is worth reminding couples that despite conceiving through IVF, they are not absolutely infertile (sterile) unless there is unequivocal azoospermia or tubal obstruction. Regarding fallopian tubes, it can be a mistake for any couple to embark on sterilisation procedures in the first few years after a child is born or if either party is relatively young (say mid-30s or less). The postnatal visit is also a time to address any general health issues and prepare for future fertility management if required.

Importantly, anxiety and depressive illnesses are more common among IVF women and should be kept in the back of one's mind during the postnatal period (as it is throughout pregnancy). Understandably, there is such a long build-up to delivery that there can be concurrent feelings of dissonance afterwards. While generally mild, these affective conditions can be severe and include psychosis. Often, IVF women forgo essential medication in the mistaken belief they are improving conception success or helping their babies. As a general rule, antidepressants are best continued in the postnatal period. It can be a taxing time for even the most mentally robust individuals.

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Long-term issues for mother and baby

The health of children born after assisted reproductive technology (ART) is one of the most important outcome parameters of procedure quality. IVF is generally safe and medical complications rare. However, as with any medical procedure, there are some possible health effects. It is, understandably, difficult to determine whether these are actual IVF-related health effects or an inherent result of the subfertile population — studies continue.

The rate of congenital anomaly in children conceived by IVF remains a little higher than in spontaneously conceived children. Recent data from South Australia, showing a similarly increased congenital anomaly rate in the naturally conceived siblings of IVF children, suggest this risk is predominantly related to the genetic health of the parents requiring IVF rather than the IVF treatment per se.

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 intracytoplasmic sperm injection.[14] Notably, this risk is not attributable to the increased risk of congenital anomalies associated with multiple birth, since the excess risk remains high among singletons.

In a large Australian study, the crude total malformation rate in ART children (including malformations diagnosed from the 20th gestational week) was 8.3% vs 5.8% in the background population — adjusted odds ratio of 1.28 (AOR).15 However, in singleton newborns from fresh-embryo IVF compared with the background population, the AOR was 1.06, demonstrating no increased overall risk of birth defects after IVF.

It has been reported that genomic imprinting — an epigenetic phenomenon by which expression of a gene is determined by its parental origin and only one allele of the imprinted gene is expressed — may be disrupted during IVF. The absolute risk of imprinting disorders after assisted reproduction is less than 1%. It has been reported that Beckwith–Wiedemann syndrome (an imprinting disorder) has a six-fold increase in incidence against a background incidence of about 1.3 per 100,000 newborns, and the incidence of Angelman syndrome is also increased.

Ultimately, there is reassurance in the fact that IVF babies are not singled out by paediatricians for special attention or follow–up; nevertheless, the oldest IVF baby is now 36 years old, and very long-term data, particularly multigenerational data, are not available at this point in time. Like all medical treatments, judicious use is essential.

Case study

KATIE T, aged 40, and her husband, 45, conceive on their third IVF cycle after two years of primary infertility. They present to discuss pregnancy care at eight weeks' gestation following a reassuring seven-week ultrasound. The subfertility factors identified were abnormal sperm morphology (0% normal, but a good count of 21 million/mL) and diminished egg quality related to female age. Each cycle was stimulated because no embryos were available to freeze as a result of diminished ovarian reserve.

The immediate task is to review overall fitness for pregnancy, order standard antenatal tests and discuss booking at a hospital. Folate should continue as well as any prescribed hormonal support. The clinic nurses will be following set protocols for the latter. Screening for Down syndrome, and other chromosomal conditions, is always advisable — but particularly so in consideration of Katie T's age. Her risk of a trisomy 21 live birth is one in 84. She opts for NIPT blood testing at 10 weeks but is also advised to have a 12-week ultrasound and serology. All are reassuring.

Gestational diabetes is identified at 27 weeks' gestation. This is, fortunately, managed by dietary control alone.

Katie T has an elective caesarean at term. At this point, she is unfavourable for induction. The risk of intrauterine death beyond term (a one in 247 probability) is recognised. She and her husband decide they want the certainty of a scheduled caesarean. All goes well, and a healthy, albeit borderline small-for-dates, 2.85kg baby girl is delivered. The obstetrician describes a thin, calcified placenta with meconium liquor (ie, there is evidence of early placental insufficiency, and the timely delivery has been fortuitous).

Katie T returns five-weeks post-partum with irregular bleeding. The bleeding is only two or three pads a day, and there is no abdominal tenderness. Katie T looks tired but otherwise well. She has normal observations and good conjunctival colour. As this loss is within reasonable limits, Katie T is reassured and encouraged to continue the oral iron prescribed in the third trimester. Of more significance is evidence of post-partum depression. Katie T reports an enormous emotional build-up over the three IVF cycles. The initial euphoria was replaced with a sense of inadequacy and despair. Poor feeding patterns and extreme fatigue are greatly compounding the situation. These problems are addressed, including involvement of a midwife expert in lactation. Katie T is asked to return in three weeks.

At the next visit, eight-weeks post-partum, Katie T is in much better spirits. On discussion regarding contraception, Katie T expresses a strong desire to have a second child but "not for a while". As her psychological state is now sound, it is strongly emphasised that embarkation on another IVF cycle in relatively quick time is, unfortunately, important given her age, poor ovarian reserve and limited embryo yield. She and her husband do not have the luxury of a number of frozen embryos (time-locked at the age of egg collection). Although there are possible physical, psychological and financial benefits in waiting a year post-caesarean, the advice at this visit is to wean by six-months post-partum and to call the specialist at this point with a view to commencing a new stimulated cycle in 6-8 weeks' time. A follow-up two-hour glucose tolerance test for two months' time is arranged.

References

1. Macaldowie A, et al. Assisted reproductive technology in Australia and New Zealand 2012. Sydney: National Perinatal Epidemiology and Statistics Unit, University of New South Wales, 2014.
2. Petterson B, et al. Twins, triplets, and cerebral palsy in births in Western Australia in the 1980s. BMJ 1993; 307(6914):1239-43.
3. Li Z, et al. Australia's mothers and babies 2011. Perinatal statistics series no. 28. Cat. no. PER 59. Canberra: AIHW National Perinatal Epidemiology and Statistics Unit, 2013.
4. McLernon DJ, et al. Clinical effectiveness of elective single versus double embryo transfer: meta-analysis of individual patient data from randomised trials. BMJ 2010; 341:c6945.
5. Sovio U, et al. First trimester PAPP-A and the risk of fetal growth restriction. American Journal of Obstetrics & Gynecology 2014; 210(1 Suppl):S112.
6. Raatikainen K, et al. Prolonged time to pregnancy is associated with a greater risk of adverse outcomes. Fertility and Sterility 2010; 94(3): 1148-51.
7. Tsoumpou I, et al. Failed IVF cycles and the risk of subsequent preeclampsia or fetal growth restriction: a case-control exploratory study. Fertility and Sterility 2011; 95(3):973-8.
8. Basso O and Olsenm J. Subfecundity and neonatal mortality: longitudinal study within the Danish national birth cohort. BMJ 2005; 330(7488):393-4.
9. Kalra SK, et al. Ovarian stimulation and low birth weight in infants conceived through in vitro fertilization. Obstetrics & Gynecology 2011; 118(4):863-871.
10. Cooper AM, et al. Smaller fetal size in singletons after infertility therapies: the influence of technology and the underlying infertility. Fertility and Sterility 2011; 96(5):1100-06.
11. Letur-Könirsch H. Annual meeting of the European Society of Human Reproduction and Embryology, 2014.
12. Gordon A, et al. Risk factors for antepartum stillbirth and the influence of maternal age in New South Wales Australia: A population based study. BMC Pregnancy and Childbirth 2013; 13:12.
13. Salihu HM, et al. Childbearing beyond maternal age 50 and fetal outcomes in the United States. Obstetrics & Gynecology 2003; 102(5 Part 1):1006-14.
14. Buckett WM, et al. Obstetric outcomes and congenital abnormalities after in vitro maturation, in vitro fertilization, and intracytoplasmic sperm injection. Obstetrics & Gynecology 2007; 110(4):885-891.
15. Davies, MJ, et al. Reproductive technologies and the risk of birth defects. New England Journal of Medicine 2012; 366:1803-13.

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Conclusion

PREGNANCY management following IVF success needs to take into account three main issues: unique aspects of care in the first few weeks related to early monitoring of a 'precious' pregnancy; hormonal support requirements; and the, now uncommon, occasional development of OHSS. There is also the consideration of a raised relative risk of congenital abnormalities, relatively poorer statistics for fetal welfare, premature delivery and other pregnancy complications. Many of these raised risks may reflect the IVF patient cohort rather than intrinsic IVF risks. The women are often older and more likely to have concomitant conditions, and there may be male factors at play. Women with IVF pregnancies are often, understandably, very risk averse in terms of delivery timing and modalities of care, particularly when the prospect of establishing another successful pregnancy is poor. Beyond delivery of an IVF baby, establishment of an ongoing fertility management plan will reduce the common problem of subsequent failure to conceive related to advancing female age.

Summary

- Early pregnancy failure is common but particularly traumatic for IVF couples.
- Ectopic IVF pregnancies can occur.
- IVF clinic regimes for hormonal support are very important because natural hormone production, particularly of progesterone, is often insufficient. Each type of cycle will have an early pregnancy protocol.
- OHSS occurs in about 1% of IVF pregnancies. While usually mild, severe cases can be life-threatening.
- Long-haul travel is particularly ill-advised until after a seven-week viability ultrasound and is discouraged in pregnancy generally.
- The novel capacity to 'panel test' parents for a large range of inheritable diseases will alter the nature of early pregnancy screening. The risk of many recessive disorders can be flagged.
- NIPT for Down syndrome can be done from 10 weeks' gestation.
- Ultrasound and serological screening for Down syndrome are still recommended, even when an embryo has been described as 'aneuploid' by preimplantation genetic diagnosis.
- Multiple-pregnancy rates have declined with the rise of SET.
- IVF women have mildly increased relative risks of LBW and preterm labour. IVF women also have independent risk associated with age and the fact they are subfertile.
- For women with a low chance of conceiving again, risks related to late intrauterine death and labour events carry increased gravity.
- Should another child be desired, a timely return to further IVF is essential for women with declining ovarian reserve.

Declaration of interest statement

The author holds shares in Genea.

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How to Treat Quiz

Part II – Pregnancy after IVF success — 27 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 early pregnancy are correct?

a) About 10% of early human conceptions are aneuploid and destined to fail.
b) Ectopic pregnancy has an incidence of 1.3% in IVF gestations.
c) Miscarriages in IVF pregnancies occur at twice the age-related rate as naturally conceived pregnancies.
d) In terms of early hormonal support, particular focus is placed on ensuring sufficient progesterone to nurture an early pregnancy.

2. Which THREE statements regarding ovarian hyperstimulation syndrome (OHSS) are correct?

a) It is a widely recognised complication of ovarian stimulation for IVF or ovulation induction.
b) Women with PCOS have an increased risk of developing OHSS.
c) A thromboembolic event is the most dangerous risk among women with markedly raised oestrogen levels.
d) The worst of OHSS is usually over by the end of the first trimester.

3. Which THREE statements are correct?

a) Multiple pregnancy has a higher risk of cerebral palsy.
b) Most embryo transfers in Australia use double-embryo transfer (DET) as opposed to single-embryo transfer (SET), with a view to increasing the success rate of IVF.
c) Elective SET results in a higher chance of delivering a term singleton live birth compared with DET.
d) Triplet deliveries are a rare event in Australia for both natural and IVF conceptions.

4. Which pathology tests are done at the booking visit?

a) FBC, blood group and antibody screen
b) Rubella antibody status and syphilis serology
c) MSU
d) Hepatitis B and hepatitis C serology

5. Which TWO statements are correct?

a) A single blood test can identify the carrier status of prospective parents for certain conditions.
b) Cystic fibrosis, an autosomal dominant condition, has a one in 2500 incidence in the Caucasian population.
c) A new maternal test (NIPT) for Down syndrome screening is available from 10 weeks' gestation.
d) NIPT can accurately identify Down syndrome, and no further confirmation is required.

6. Which THREE statements regarding risk in IVF pregnancy are correct?

a) Risk of gestational diabetes is increased in the IVF population secondary to an increased average maternal age.
b) The second trimester is the one of greatest risk to both mother and fetus in the case of IVF pregnancy.
c) IVF pregnancies have a mildly increased relative risk of low birth weight (LBW), fetal growth restriction (FGR), preterm birth, and perinatal morbidity and mortality.
d) Premature labour is more likely in IVF pregnancy.

7. Which TWO statements are correct?

a) Singleton infants born after IVF are at an increased risk of LBW.
b) Donor-egg IVF conceptions have a raised risk of pre-eclampsia.
c) In 2011, women aged 40 and over made up 15% of all women giving birth compared with 3.0% in 2002.
d) Advanced maternal age does not impact on the risk of fetal loss, provided the IVF and pregnancy are well managed.

8. Which THREE statements regarding the possible consequences of hypertension on a pregnancy in an older woman are correct?

a) Pre-eclampsia
b) Placental abruption
c) Stillbirth
d) Pulmonary embolus

9. Which THREE statements regarding the follow-up after delivery of a child conceived by IVF are correct?

a) Australian IVF live delivery per initiated cycle is 24.8% in women aged 30-34 while the chance at a current age of 37 is reduced by nearly a third.
b) The aneuploidy rate will be relatively high in frozen embryos that are collected after the age of 35.
c) Women seeking to conceive a second child by IVF soon after a child born by IVF may safely breastfeed the first child with no impact on the success of the second attempt.
d) Anxiety and depressive illnesses are more common among IVF women.

10. Which TWO statements are correct?

a) About 3.8% of all babies born in Australia are now the result of IVF technology.
b) IVF pregnancies have statistical variance from other pregnancies on a number of measures.
c) The risk of LBW and preterm delivery doubles in older mothers, and intrapartum complications, such as increased labour times and a greater chance of caesarean and operative delivery, are also raised.
d) Studies have failed to demonstrate a difference in the rates of congenital anomalies between IVF babies and those conceived spontaneously.

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

GPs may see patients with concussion immediately after injury on the sports field or may see them several days afterwards, after they have been assessed in an emergency department. Concussion management is individualised. This includes baseline concussion assessment and monitoring of return to work/school and sport. The author is **Dr Ryan Kohler** HeadSmart™ Sports Concussion Programme (Founder), HeadSmart Concussion & Sports Injuries Centre (Founder), Associate Professor University of Canberra and Sports Concussion Programme South Africa (Co-Founder).