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Review

Antenatal management of singleton pregnancies conceived using assisted reproductive technology

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Key content

- Use of assisted reproductive technology (ART) to achieve conception is increasing worldwide, and while the majority of resulting pregnancies will have a normal outcome, not all do.
- Assisted conceptions are at increased risk of maternal and fetal complications – many of which may be underappreciated or indeed overappreciated by those who go on to look after pregnant women.
- Healthcare professionals involved in the antenatal care of women who have conceived using ART must understand the potential risks, their significance and how best to monitor them.

Learning objectives

- To understand the maternal complications associated with ART, including ovarian hyperstimulation syndrome, miscarriage, ectopic pregnancy, pregnancy-induced hypertension, pre-eclampsia, gestational diabetes and venous thromboembolism.
- To understand the fetal complications associated with ART, including genetic and chromosomal disorders, structural abnormalities, growth restriction, stillbirth and preterm labour.
- To establish an evidence-based approach to the antenatal management of singleton pregnancies conceived using ART.

Keywords: antenatal / assisted reproductive technology / complication / obstetric / singleton

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Introduction

Since the birth of the first baby conceived by in vitro fertilisation (IVF) in 1978, more than 5 million babies have been born as a result of assisted reproductive technology (ART). Furthermore, demand for ART is increasing, and in most developed countries, 1–5% of the babies born have been conceived through IVF.

Although the majority of pregnancies conceived following ART have a normal outcome, a significant minority do not. Assisted conceptions are at increased risk of maternal and fetal complications (Table 1), but it is not clear whether this is a consequence of the ART procedures, or of the innate characteristics of the women who undertake them.

Healthcare professionals involved in the antenatal management of pregnancies conceived using ART must understand the potential risks and how best to manage them. Since the care of multiple pregnancies has been covered elsewhere, this Review focuses solely on the antenatal management of singleton pregnancies conceived using ART.[1]

Early pregnancy complications

Miscarriage and ectopic pregnancy are common complications of early pregnancy. Although not unique to assisted conceptions, these diagnoses often come as a shock to women undergoing treatment and their partners. Psychological sequelae can therefore be profound.[2] In the UK, the law requires fertility clinics to offer counselling when individuals seek treatment to create embryos in vitro. This counselling should be available throughout the treatment processes – and afterwards, if requested. By contrast, ovarian hyperstimulation syndrome (OHSS) is unique to fertility treatment. All women, and particularly those at increased

Table 1. Summary of the risks and recommendations for the antenatal management of singleton pregnancies conceived using assisted reproductive technology

Condition	Incidence/risk	Recommendations
Early pregnancy complications		
OHSS	Mild: incidence ~33% Moderate–severe: incidence 3.1–8%	• Establish evidence-based protocols for assessment and management of women • Admitting centre to inform fertility clinic about admission and diagnosis • Fertility clinic to report all cases of severe/critical OHSS to Human Fertilisation and Embryology Authority
Miscarriage	Incidence ~15–20%	• Manage as per spontaneous conception • **Women should have access to specialist counsellors before, during and after ART**
Ectopic pregnancy	Incidence ~1.4%	• Manage as per spontaneous conception • **Women should have access to specialist counsellors before, during and after ART**
Maternal complications		
Pregnancy-induced hypertension/pre-eclampsia	RR 1.49 (95% CI 1.39–1.59) Absolute increase in risk ~2%	• Risk assessment as per local and national guidelines • ART is not an indication for aspirin prophylaxis in the absence of other risk factors (which may be more common in women requiring ART to conceive)
Gestational diabetes mellitus	RR 1.48 (95% CI 1.33–1.66) Absolute increase in risk ~1%	• Risk assessment as per local and national guidelines • In the UK, ART is not an indication for a glucose tolerance test in the absence of other risk factors
Venous thromboembolism	Highest in first trimester	• Risk assessment as per local and national guidelines • In the absence of other risk factors, no need for anticoagulation
Fetal complications		
Structural abnormalities	30–40% increased incidence Absolute risk still low: 6.5–7%	• No additional surveillance recommended
Fetal growth restriction	OR 1.6 (95% CI 1.3–2.0)	• No additional surveillance in absence of other risk factors (which may be more common in women requiring ART to conceive)
Stillbirth	OR 2.4 (95% CI 1.59–3.63)	• Consider induction of labour at term
Preterm labour	~11.2% May be iatrogenic	• No additional surveillance recommended
Placental complications		
Placenta praevia	OR 3.76 (95% CI 3.09–4.59)	• No additional surveillance recommended
Placenta accreta	OR 2.27 (95% CI 1.79–2.87)	• No additional surveillance recommended
Placental abruption	OR 1.87 (95% CI 1.7–2.06)	• No additional surveillance recommended
Vasa praevia		• If low lying placenta diagnosed during anomaly scan, transvaginal ultrasound with colour Doppler to exclude vasa praevia should be undertaken

ART = assisted reproductive technology; CI = confidence interval; OHSS = ovarian hyperstimulation syndrome; OR = odds ratio; RR = relative risk

risk, should be counselled about this condition both before consent to treatment is given and before treatment is provided or continued. Diagnosis and management of these complications has been covered elsewhere,[3–5] hence a detailed discussion is not included here. However, there are a few pertinent features about which those involved in the clinical management of assisted conceptions ought to be aware.

Ovarian hyperstimulation syndrome

The incidence of OHSS varies between different types of fertility treatment, with treatments involving greater degrees

of ovarian stimulation being associated with a higher incidence. Following conventional IVF, mild OHSS has been estimated to affect around one-third of cycles, while the combined incidence of moderate or severe OHSS varies from 3.1% to 8.0%.[6] In 2010, data from 25 European countries found the incidence of hospitalisation caused by OHSS to be 0.3%.[7]

Acute units, where women with OHSS are likely to present, should establish agreed evidence-based protocols for the assessment and management of these women and ensure that they have access to appropriately skilled clinicians with experience in the management of this condition.[3] In addition, the admitting centre should inform the originating clinic about the admission of women with OHSS. Fertility clinics in the UK have a legal obligation to report all cases of severe and critical OHSS to the Human Fertilisation and Embryology Authority (HFEA). This duty lies with the 'Person Responsible' of the licensed centre providing the fertility treatment.

Clinicians should be aware that there is some evidence to suggest an increased risk of pregnancy-induced hypertension (PIH) and preterm labour (PTL) in pregnancies complicated by severe OHSS.[8–10] Furthermore, OHSS is also a risk factor for venous thromboembolism (VTE), with the incidence of thrombosis estimated to lie between 0.7% and 10%.[11] Thrombosis in women with OHSS frequently affects upper body sites and/or the arterial system, and women may present with symptoms several weeks after the apparent resolution of OHSS. Thromboprophylaxis is recommended for women with severe OHSS or other risk factors for VTE. The duration of treatment should be based on individual risk factors and whether or not conception occurs. If conception occurs, thromboprophylaxis should be continued until at least the end of the first trimester.[3]

Miscarriage

The miscarriage rate among pregnancies following ART is estimated to be approximately 15–20%[12,13] and, like spontaneous conceptions, increases with increasing age.[14] The specific cause of subfertility may also affect the miscarriage rate: women with, for example, certain congenital uterine anomalies,[15] fibroids[16] and some endocrine disorders,[17] have higher rates of miscarriage than do those without. Although women who miscarry following ART can generally be reassured that they are more likely to have a live birth in subsequent cycles than if they had never conceived,[18] as in the general population, some women undergoing ART may also experience recurrent miscarriage. The management of women with both sporadic and recurrent miscarriage in the ART population is no different to that of women in the general population and has been covered elsewhere.[5,19]

Subclinical hypothyroidism

Although the relationship between overt hypothyroidism and adverse pregnancy outcomes including miscarriage, pre-eclampsia, gestational diabetes mellitus (GDM), PTL and cognitive delay in children is well established, and the benefit of treatment with levothyroxine for such women is clear, the same is not true for subclinical hypothyroidism (SCH).

Evidence that SCH causes adverse pregnancy outcomes is inconsistent and conflicting. Many, but not all, observational studies that have examined the effect of SCH on pregnancy-related outcomes have associated it with multiple adverse outcomes.[20–22] A recent meta-analysis incorporating 18 cohort studies found that pregnant women with untreated SCH are at increased risk of miscarriage, placental abruption, premature rupture of the membranes and neonatal death compared with euthyroid women.[23]

Current guidelines therefore recommend treatment with levothyroxine in pregnant women with SCH,[24,25] but there is insufficient evidence that this approach improves clinical outcomes.[26] A recent study including 5405 pregnant women with SCH demonstrated that, compared with women with SCH receiving no treatment, treatment with levothyroxine was associated with a decreased risk of miscarriage but an increased risk of PTL, GDM and pre-eclampsia.[27] Another randomised study, incorporating 677 pregnant women (sufficient participation to achieve a power of at least 80% and a two-sided type I error rate of 5%) diagnosed with SCH, demonstrated that treatment with levothyroxine did not result in significantly better cognitive outcomes in children at 5 years of follow-up.[28] A small study (n = 64), including women undergoing ART, demonstrated that in women with SCH, treatment with levothyroxine decreased miscarriage and increased live-birth rates, while not affecting clinical pregnancy rates.[29]

The diagnosis and management of SCH in women attempting a pregnancy is controversial, and a detailed discussion is beyond the remit of this Review. The American Society of Reproductive Medicine has published guidelines with pragmatic recommendations that attempt to take into consideration the current limited evidence base.[30]

Ectopic pregnancy

This risk of an ectopic pregnancy following ART is approximately 1.4%.[31] Many fertility clinics, in an attempt to reassure women (and their partners) and diagnose complications early, therefore advocate an early ultrasound scan to confirm pregnancy location and viability. In asymptomatic women with no previous history of an ectopic pregnancy, the optimal time for this scan is at around 7 weeks of gestation.[32] Heterotopic pregnancies are also more common following ART. This must be considered as a differential diagnosis when a patient presents with symptoms of an ectopic pregnancy and two embryos are

transferred. Careful ultrasound examination of the adnexa is required, even in the presence of an intrauterine pregnancy. Management of ectopic pregnancies includes conservative, medical and surgical approaches and should follow local protocols based on national guidelines[4] and take into consideration the woman's preference following an informed decision.

Of note, when considering surgical management for a tubal ectopic pregnancy in women with a history of fertility-reducing factors, salpingotomy should usually be considered (because of the higher subsequent intrauterine pregnancy rates observed).[4] In women who are reliant on ART to conceive, however, the fallopian tubes are redundant. Therefore, a salpingectomy may actually be preferential (depending on the cause of subfertility) because it eliminates the possibility of a subsequent ectopic pregnancy on that side without compromising fertility. Concerns have been raised about a potential reduction in ovarian reserve following tubal surgery, but several studies have suggested these to be unfounded.[33] Surgeons must, however, strive to avoid inadvertent damage to the gonadal artery during salpingectomy so as not to unnecessarily disrupt blood supply to the ovary.

'Add-ons' and pharmacological interventions to support a pregnancy

In the last decade, a plethora of IVF adjuncts or 'add-ons' have been introduced, many without robust evidence that they increase the chance of a live birth or have any real benefit in terms of health and wellbeing of the child. These have been discussed in detail[34] and summarised[35] elsewhere.

Similarly, there are numerous pharmacological interventions purported to improve clinical pregnancy and live-birth rates in women undergoing ART. However, for most of these there is insufficient evidence to recommend their use. Table 2 summarises some of the more commonly encountered medications and the evidence, if any, behind their use. Obstetricians may encounter women on these (and other) medications prescribed by their colleagues in reproductive medicine for which there is no, or a limited, evidence base. In these difficult situations we recommend liaison with the initial prescriber.

Maternal complications

Pregnancies resulting from ART may have increased risks for maternal medical complications, especially PIH, pre-eclampsia, GDM and VTE. These risks largely arise owing to the characteristics of those undergoing ART and are most marked in older women (aged >35 years), women with a high body mass index (BMI; >30 kg/m^2) or polycystic ovary syndrome (PCOS) and in multiple pregnancies, as well as pregnancies that are created from oocyte, sperm or embryo donation.

Pregnancy-induced hypertension and pre-eclampsia

According to a systematic review and meta-analysis incorporating 15 cohort studies, women who become pregnant as a consequence of ART are more likely to develop PIH and pre-eclampsia than those with a spontaneous conception (relative risk [RR] 1.49, 95% confidence interval [CI] 1.39–1.59). The absolute increase in risk for hypertensive complications was approximately 2%.[36] Women who become pregnant as a consequence of oocyte donation appear to be at slightly greater risk of PIH than women undergoing ART using autologous oocytes (matched odds ratio [OR] 1.50, 95% CI 1.02–2.20).[37]

Women who become pregnant as a consequence of ART should, like all women, have a risk assessment at booking. Those considered to be at high risk of PIH or pre-eclampsia should be offered low-dose aspirin (75 mg) from 12 weeks of gestation until delivery.[38]

Women considered to be at high risk of pre-eclampsia include those with one major risk factor or more than one moderate risk factor.[38] Major risk factors are hypertensive disease during a previous pregnancy, chronic kidney disease, autoimmune diseases, diabetes and chronic hypertension. Moderate risk factors include first pregnancy, maternal age ≥40 years, pregnancy interval >10 years, BMI >35 kg/m^2, family history of pre-eclampsia and multiple pregnancy.

Women with any of these risk factors, irrespective of whether they meet the criteria for prophylaxis, should also have a plan for closer maternal and fetal surveillance; for example, at least every 3 weeks between 24 and 32 weeks of gestation, increasing to every 2 weeks thereafter.[39]

Although at slightly increased risk, women who become pregnant as a consequence of ART are not at high risk of PIH or pre-eclampsia. However, compared with the general population, women requiring ART to conceive may be more likely to have one major or two moderate risk factors.

Gestational diabetes mellitus

Whether or not ART increases the risk of GDM is controversial, with some studies reporting an increased risk and others not.[40] This is probably because there are different definitions used to diagnose GDM.[41] A recent systematic review incorporating six studies reported a RR for GDM of 1.48 (95% CI 1.33–1.66) in assisted compared with spontaneous conceptions,[36] equivalent to an absolute increase in risk of approximately 1%.

ART per se is not an indication for a glucose tolerance test (GTT) in pregnancy. Women who become pregnant as a consequence of ART should therefore be risk-assessed as per national or local guidelines. In 2010, the International Association of Diabetes and Pregnancy Study Group concluded that all women (irrespective of mode of conception) should have a GTT performed at 24–28 weeks

Table 2. Pharmacological interventions purported to support a pregnancy, the evidence behind their use and recommendations for practice

Medication	Population	Evidence	Recommended use
Aspirin	Women with unexplained RM	No benefit[80] Some evidence of reduction in LBR	No
G-CSF (NT100)	Women with RIF, persistently thin endometrium or RM	Limited evidence of benefit[81] Results from RESPONSE trial awaited	No
hCG	Women with RM	Equivocal[82] No evidence of harm	No
	Women with threatened miscarriage	No benefit[83]	No
Heparin	Women with antiphospholipid syndrome and RM	Reduces miscarriage rate[84]	Yes
	Women with RM and inherited thrombophilia	Limited evidence of benefit Results from ALIFE2 awaited	No
	Women with RM	No benefit[85]	No
	Women undergoing ART	Limited evidence of benefit of peri-implantation administration[86]	No
Immunotherapy	Women with RIF or RM	No benefit[87] Associated side effects including anaphylaxis (IVIg), immunosuppression and granulomatous disease (TNFα)	No
Progesterone	Women undergoing ART (luteal phase only)	Increases clinical pregnancy rate and LBR[88]	Yes
	Women with RM	No benefit[89]	No
	Women with threatened miscarriage	Limited evidence of benefit[90] Results from PRISM study awaited	No
Steroids	Women with RM and raised uNK cells	Limited evidence of benefit[91]	No

ART = assisted reproductive technology; CPR = clinical pregnancy rate; G-CSF = granulocyte colony stimulating factor; hCG = human chorionic gonadotropin; IVIg = intravenous immunoglobulin; LBR = live-birth rate; RIF = recurrent implantation failure; RM = recurrent miscarriage; TNFα = tumour necrosis factor alpha; uNK = uterine natural killer cell

of gestation.[42] In the UK, however, the National Institute for Health and Care Excellence (NICE) recommends that a GTT is performed only in women who are at high risk.[43]

The prevalence of GDM is twice as high among women with PCOS than among women without (OR 2.32, 95% CI 1.88–2.88).[44] Clinicians may therefore consider offering screening for GDM to women who have been diagnosed as having PCOS before pregnancy.

Venous thromboembolism

ART has been shown to double the risk of VTE during pregnancy.[45] The risk is particularly great in the first trimester (when it is approximately four-fold).[45] Unlike PIH, pre-eclampsia and GDM, ART is itself considered to be a risk factor for developing VTE in pregnancy. In the absence of any other risk factors, however, prophylactic anticoagulation with low molecular weight heparin is not required.[46] Prophylaxis is recommended from the first trimester onwards if there are an additional three risk factors and from 28 weeks of gestation onwards if there are an additional two risk factors. Additional risk factors include BMI >30 kg/m^2, age >35 years, parity ≥3, smoking, gross varicose veins, immobility, family history of unprovoked or estrogen-provoked VTE in a first-degree relative, low-risk thrombophilia and multiple pregnancy.[46] Temporary factors including OHSS, hyperemesis, dehydration, surgery, systemic infection, immobility and long-distance travel also increase the risk of VTE and should prompt initiation of thromboprophylaxis until the risk period is passed.

Fetal complications

Since the introduction of ART, there has been concern regarding its effects on the fetus. Over the years, as more pregnancies have occurred and outcomes have been reported, much of this fear has abated. While some complications are more common in fetuses arising as a consequence of ART,[47] it is not known whether this is because of the ART procedure

itself, the underlying subfertility, the increased incidence of multiple pregnancies, advanced maternal age or poor gamete quality.

Fetal genetic and chromosomal disorders and structural abnormalities

Numerous studies have attempted to determine whether the incidence of fetal structural abnormalities is higher in children conceived following ART than in those conceived spontaneously. Although most report a significantly increased rate of structural abnormalities (including anorectal malformations, congenital cardiac lesions, and nervous system and genital structural abnormalities) in the assisted conception cohorts,[48,49] with odds ratios ranging from 1.37 (95% CI 1.26–1.48) to 2.01 (95% CI 1.49–2.69),[50] the type and frequency of abnormalities found is inconsistent. Furthermore, some studies,[51] but not all,[50] suggest that congenital abnormalities are more common in children conceived following intracytoplasmic sperm injection than standard IVF.

The risk of unrecognised chromosomal abnormalities is higher in those requiring ART than in the general population. In oligozoospermic men, the incidence of autosomal translocations or inversions is 4.6–13.7%[52] and the incidence of microdeletions of the Y chromosome is 5–15%.[53] This is of particular significance in oligozoospermic males who proceed with treatment without having a formal karyotype undertaken: subtle Y chromosomal genetic defects are associated with minor anomalies of the male genitalia, including hypospadias. Women who require ART may be seven times more likely to have reciprocal balanced translocations than are those who do not.[54] Although still extremely rare, there are also concerns regarding an excess of fetal imprinting disorders such as Angelman and Beckwith–Weidermann syndromes following ART.[55]

Despite the reported 30–40% increased incidence of fetal structural abnormalities observed in individuals undergoing ART, the absolute risk is still very low (6.5–7% versus 5%)[56]; hence, in the UK, no additional surveillance is recommended other than a routine anomaly ultrasound scan undertaken at 18–20^{+6} weeks of gestation. When structural problems are encountered, the possibility of subtle chromosomal rearrangements should be considered.

Screening tests

Evidence suggests that while women who become pregnant as a consequence of ART (and their partners) are just as concerned about the risk of fetal abnormality as are those who conceive spontaneously, they are less likely to opt for Down syndrome screening or invasive testing.[57] The reasons are complex but are likely related to fears regarding procedure-related miscarriage and/or the conviction that they would continue with the pregnancy regardless of the result.

Women with assisted conceptions should be offered antenatal screening such as the first trimester combined test (nuchal translucency and maternal serum biochemistry). However, numerous studies have demonstrated that ART is associated with changes in biochemical serum screening markers, such as pregnancy-associated plasma protein A and human chorionic gonadotrophin.[58] A few studies (although not the majority) have even shown that nuchal translucency measurements may also be affected by the type of conception. It is also worth remembering that if donor eggs are used, the age of the donor should be used to calculate the a priori age-related risk, not the age of the woman undergoing treatment.

Furthermore, screening tests rely on an accurate gestational age to interpret the results of the nuchal translucency and maternal serology. Therefore, it is important that the estimated date of delivery is calculated from the date of oocyte retrieval and not the measured crown–rump length. A recent study demonstrated a systematic inaccuracy in first trimester crown–rump length/gestational age charts, which consistently overestimate the gestation of IVF pregnancies in which the exact date of conception is known.[59] This may have implications for the reliability of first trimester screening (by increasing the false positive rate), but translating this information into clinical practice is difficult. The use of cell-free fetal DNA (from maternal plasma) as a 'non-invasive prenatal test' to screen pregnancies for trisomies 13, 18 and 21 is becoming increasingly available. This test is extremely accurate, with weighted pooled detection rates of 99.2% (95% CI 98.5–99.6%), 96.3% (95% CI 94.3–97.9%) and 91.0% (95% CI 85.0–95.6%) and false positive rates of 0.09% (95% CI 0.05–0.14%), 0.13% (95% CI 0.07–0.20%) and 0.13% (95% CI 0.05–0.26%) for trisomies 21, 18 and 13, respectively,[60] and is not associated with a risk of miscarriage.

Growth restriction

There is conflicting evidence regarding the occurrence of fetal growth restriction in assisted conceptions, most likely because it is difficult to define and, prior to 2016, there was no consensus.[61] Several cohort studies and meta-analyses have reported that fetal growth can be reduced,[36,62,63] but most use low birthweight as evidence of growth restriction rather than serial scan measurements demonstrating a tailing-off of fetal growth. The increased rates of fetal growth restriction observed are most commonly attributed to abnormal placentation.

Interestingly, however, one study that directly compared children conceived via ART with their spontaneously conceived siblings found no evidence of decreased birthweight in the ART group.[64] Hence, the underlying

cause of subfertility may account for more of the variation in birthweight than the mode of conception.[49]

Several well-powered studies have also observed a higher average birthweight in children conceived using ART who were the result of frozen rather than fresh embryo transfer.[51] This phenomenon may be related to the baseline characteristics of the women and their partners who had surplus embryos to freeze, or to the fact that the intrauterine environment is less likely to be acutely influenced by hormonal stimuli.[65]

In the UK, IVF is considered to be a minor risk factor for fetal growth restriction (OR 1.6, 95% CI 1.3–2.0)[62] and, as such, in the absence of any other risk factors, increased surveillance is not currently recommended.[66] However, maternal age ≥35 years (OR 1.4, 95% CI 1.1–1.8),[67] nulliparity (OR 1.89, 95% CI 1.82–1.96) and a BMI of between 25 and 29.9 kg/m^2 (OR 1.2, 95% CI 1.1–1.3), all of which are relatively common in those seeking ART, are also minor risk factors for fetal growth restriction (Figure 1). In the presence of three or more minor risk factors, a uterine artery Doppler at 20–24 weeks of gestation and assessment of fetal size and umbilical artery Doppler in the third trimester is indicated; this may be the case for a significant proportion of assisted conceptions.[66] Furthermore, maternal age ≥40 years is considered to be a major risk factor for fetal growth restriction (OR 3.2, 95% CI 1.9–5.4)[67] and serial assessment of fetal size and umbilical artery Doppler is recommended from 26–28 weeks of gestation in these women, irrespective of how they conceived.

Stillbirth

There is some evidence that, compared with spontaneous conceptions, assisted conceptions are at an increased risk of stillbirth.[62] However, determining to what extent the ART procedures themselves are responsible for this is complex, given that stillbirth rates appear to be increased in women with a history of subfertility regardless of whether ART is utilised[68] and there are high rates of ART usage in women who have previously experienced a stillbirth. Furthermore, perinatal death rates are comparable among sibling pairs conceived spontaneously or via ART.[64] Despite this, data from meta-analyses show, even in singleton pregnancies, an increase in perinatal mortality following ART of up to 2.4-fold (OR 2.4, 95% CI 1.59–3.63).[62]

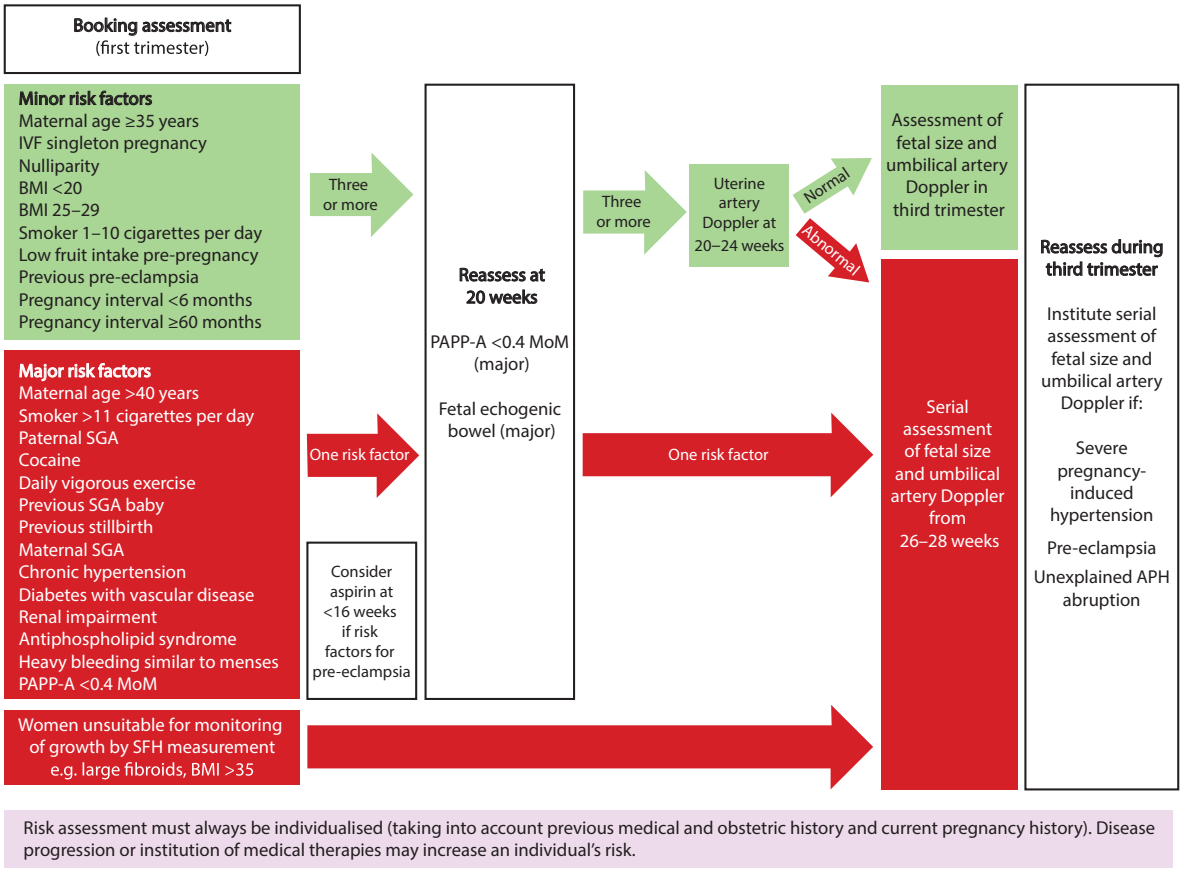

Figure 1. Screening for a small-for-gestational-age fetus.[66] APH = antepartum haemorrhage; BMI = body mass index; IVF = in vitro fertilisation; MoM = multiples of median; PAPP-A = pregnancy-associated plasma protein-A; SFH = symphysial fundal height; SGA = small for gestational age.

Timing and mode of delivery

Some clinicians feel that because of the higher stillbirth rates observed in assisted conceptions, induction of labour at term should be considered. On the one hand, there is little evidence that this practice increases interventions such as emergency caesarean sections[69] and is likely to reduce perinatal mortality by limiting the length of pregnancy and hence the risk of fetal demise.[69,70] On the other hand, there has been no trial to indicate that equally good outcomes cannot be achieved following optimal surveillance, identification of risk factors and induction of labour offered routinely if the pregnancy progresses over 41 weeks.

Elective caesarean section is more common in assisted conceptions[71]; indeed NICE supports the ability of all women to choose the mode of delivery for themselves and advocates referral to an alternative clinician if the obstetrician feels unable to support a particular request.[72]

Preterm labour

Pregnancies conceived following ART are at increased risk of PTL.[36,40,62,63,73] One study including approximately 4500 singleton pregnancies resulting from ART reported incidences of very PTL (before 32 weeks of gestation) and PTL (before 37 weeks of gestation) of 2.6% and 11.2%, respectively, compared with 0.7% and 5.4% in the general population.[49] This increase in risk, which is estimated to be at least double that occurring in spontaneously conceived pregnancies, is of similar magnitude to a mother with a previous history of PTL.[74]

It is difficult to retrospectively distinguish between spontaneous and iatrogenic causes of PTL. Furthermore, since there is no difference in PTL rates among sibling pairs conceived spontaneously and via ART, the propensity to PTL, like fetal growth restriction, may be more associated with maternal factors (for example, congenital uterine anomalies such as canalisation defects), rather than with exposure to ART per se.[64]

While ART is undoubtedly a significant risk factor for PTL, whether spontaneous or iatrogenic, there is no current evidence to suggest that additional surveillance or interventions are beneficial in reducing the rates of PTL in these conceptions.

Placental complications

A recent systematic review and meta-analysis concluded that singleton pregnancies conceived using ART are associated with a significantly higher risk of placental anomalies, including placenta praevia (OR 3.76, 95% CI 3.09–4.59), morbidly adherent placenta (OR 2.27, 95% CI 1.79–2.87) and placental abruption (OR 1.87, 95% CI 1.70–2.06), compared with spontaneously conceived pregnancies.[75]

Compared with spontaneous conceptions, there is a higher incidence of clinically significant placenta praevia persisting until term in assisted conceptions,[40,55,63,73,76] particularly those that have involved the transfer of a blastocyst rather than cleavage stage embryo. Unlike many of the other maternal and fetal complications observed in assisted conceptions, this increase in risk is believed to be a direct effect of the ART process itself, rather than a consequence of an underlying maternal structural complication such as Asherman's syndrome.[64] Assisted conceptions occurring following transfer of a cryopreserved rather than fresh embryo are less likely to be complicated by placenta praevia.[76]

Additionally, cord insertion variants, including vasa praevia, are more common in assisted conceptions.[77] This may account for the increased incidence of fetal growth restriction in ART pregnancies. In view of the increased risk of vasa praevia in assisted conceptions and its association with severe fetal complications, if a low-lying placenta is observed during the routine anomaly ultrasound, a transvaginal ultrasound using colour Doppler should be undertaken to look for vasa praevia.

The diagnosis and management of women with placenta praevia, placenta accreta and vasa praevia has been covered elsewhere.[78,79]

Conclusions

While most assisted conceptions have a normal course, not all do. The elective transfer of a single embryo reduces many risks, but even singleton pregnancies resulting from ART are at increased risk of some maternal and fetal complications. An awareness of these risks is mostly all that is required, and assisted conceptions should be managed in the same way as spontaneous pregnancies. A thorough risk assessment is imperative, since many women undergoing ART have additional risk factors that necessitate increased monitoring.

Disclosure of interests

AR is a Trainee Representative on the Editorial Board of *The Obstetrician & Gynaecologist*. She was excluded from editorial discussions regarding the paper and had no involvement in the decision to publish. The other authors have no conflicts of interest.

Contribution to authorship

AR researched the literature and wrote the manuscript. MT, JPT and TK contributed to the content and reviewed the draft manuscript. All authors approved the final version.

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