Chapter 10
Fetal Complications During Pregnancy

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Introduction

Since the introduction of artificial reproductive technology (ART) into clinical practice in 1978 [1] there has been considerable concern regarding effects on the resulting fetus, and the long-term outcomes for the offspring. In particular, concerns were widely voiced that the 'by-passing' of normal gamete selection processes during conception would result in a much greater chance of children being born with genetic or structural anomalies. However, as more pregnancies following ART have been conceived and their outcomes reported, many of the initial fears have subsided. There have now been over five million births worldwide following the use of ART and the rates of assisted conceptions continue to rise [2]. In 2011, approximately 1.5 % of all pregnancies in the US were conceived using ART [3], hence any increase in adverse fetal outcomes resulting from the use of this technology would constitute a significant public health issue. While some perinatal complications are more common in fetuses resulting from ART, difficulties arise in many studies with defining the risk of complications that is attributable to the process of ART itself. There are a number of important confounding factors that may well contribute to adverse fetal outcomes in pregnancies conceived using ART, including the high incidence of:

- Multiple pregnancies
- Underlying subfertility

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K. Jayaprakasan, L. Kean (eds.), *Clinical Management of Pregnancies following ART*, DOI 10.1007/978-3-319-42858-1_10

- Poor gamete quality
- Advanced maternal age

All of these factors contribute to increased risk for adverse fetal outcomes independent of the actual processes of assisted conception. Nonetheless pregnancies conceived using ART do have a higher risk of fetal complications, regardless of whether these have a causal association with the use of ART or are merely associated through other indirect factors such as maternal age. Perhaps most concerning for clinicians caring for couples who have undergone assisted conception are data from meta-analyses that show an increase in perinatal mortality following ART by up to 2.4-fold (OR 2.4; CI 1.59–3.63), even in singleton pregnancies [4, 5].

This chapter aims to examine the magnitude and the nature of increased fetal complications during pregnancies conceived using ART, and where possible to disentangle the mechanisms leading to an association between mode of conception and fetal complications. Early pregnancy loss prior to fetal development and later childhood outcomes are not considered in detail here as they are discussed elsewhere.

Factors Contributing to Fetal Complications in Pregnancies Conceived with ART

One of the most important factors giving rise to fetal complications from pregnancies conceived using ART is the effect of maternal age. Higher maternal age is a risk factor for adverse fetal outcomes, regardless of mode of conception. Increased complications include a higher risk of chromosomal anomalies, intrauterine growth restriction and both iatrogenic and spontaneous preterm births [6]. Maternal age is readily ascertainable in most cohorts and is relatively easily controlled for. However, there are numerous other risk factors that are more common in older mothers that need to be accounted for in determining relative risk and these are often not adjusted for, particularly in retrospective cohorts. Pre-existing maternal medication conditions, for example hypertension and type 2 diabetes, are more common in older mothers [7]. These conditions may have an important influence on fetal complications during pregnancy, but are commonly missing data in less well-characterised cohorts.

Increased use of ART with donor oocytes has allowed pregnancy to become more common at the extremes of reproductive age, where the risks of hypertensive disease and operative delivery are much increased [8]. The effects of these adverse maternal outcomes on the fetus may be difficult to disentangle from other background risks.

Aside from maternal age, socioeconomic factors may be significantly different between populations of parents who conceive spontaneously and using ART, with one study observing more than twice the number of pregnancies conceived by ART

in the highest versus the lowest socioeconomic status groups [9]. These factors are often not controlled for when making comparisons between groups. Particularly, information regarding the father (age, smoking status, and socioeconomic factors such as occupation) is often not accounted for in retrospective cohorts, although his input both biologically and socially may be germane to successful fetal outcomes.

The extent to which adverse maternal and fetal complications of any pregnancy can be separated is limited due to the nature of the intrinsic interplay of the materno-placento-fetal axis in maintaining a successful pregnancy. It is therefore necessary to consider the incidence of adverse fetal outcomes arising indirectly through maternal complications of pregnancies conceived using ART. The rate of maternal gestational diabetes for example is increased in pregnancies conceived using ART [9–11], and may lead to important fetal complications such as macrosomia and birth trauma. Similarly, high rates of maternal complications such as pregnancy-induced hypertension, antepartum haemorrhage and pre-eclampsia [11–13] may lead to an increase in iatrogenic preterm birth, even in the absence of any direct fetal complications. The maternal consequences of ART are dealt with in detail elsewhere, but must be born in mind as they are not independent of many of the fetal complications of pregnancy.

More complicated is the role of the underlying aetiology for the parental subfertility. In many studies this is not well recorded or controlled for. Even when the categorisation of subfertility is reliably ascertained many broad categories of infertility classification, such as ‘unexplained’ will contain a multitude of different pathologies, many of which might impact on the fetal course during pregnancy. There is evidence that both maternal complications of pregnancy and immediate neonatal outcomes (as assessed by Apgar scores) are influenced by the nature of the subfertility diagnosis [14, 15].

A further difficulty in interpreting and comparing studies is that not all ART techniques necessarily carry similar risks [16] and, particularly in small studies, there is a tendency to conflate groups that are not necessarily comparable. In addition, different techniques are more suitable for particular patient groups, and there may be systematic biases between the women who underwent each treatment [16]. The use of frozen embryo transfer, for example, is often associated with a non-hormonally stimulated endometrial environment (potentially influencing implantation and placental development) and may be more likely to contain women with some selection advantage, as this group by definition has produced a surplus of good-quality embryos during a previous cycle. Hence the outcomes from frozen cycles might be expected to be marginally better than from fresh cycles [12, 17]. Concerns have been raised regarding higher rates of genetic and chromosomal abnormalities in pregnancies conceived using ICSI, particularly where testicular biopsy is used to retrieve sperm [18]; however, there is little objective evidence as yet that this is the case [19]. Studies that do not take adequate account of technique and population-related factors risk over-estimating the adverse effects of ART on fetal outcome.

Fetal Complications During Pregnancy

Fetal Genetic and Chromosomal Disorders

A considerable number of infertility treatments are undertaken in order to perform preimplantation genetic diagnosis and hence reduce the risk of passing on genetic diseases that are known to be present in the parents. However, the risk of an unrecognized chromosomal anomaly being present in the parents is higher in the population requiring fertility treatment than in the general population. Azoospermic or oligozoospermic men requiring fertility treatment have a risk of autosomal translocations or inversions of 4.6–13.7 % [20]. Female partners of males requiring infertility treatments also have a higher risk than the general population of chromosomal anomalies for reasons that are not well understood. One series has suggested a sevenfold increase in reciprocal balanced translocations in the female partners in couples undergoing assisted conception [21]. In addition to heritable autosomal rearrangements, micro-deletions of the Y chromosome are a common finding in males with oligo- or azoospermia, occurring in up to 5–15 % of cases [22, 23]. If intracytoplasmic sperm injection (ICSI) is performed (overcoming the effects of a very low sperm count), then these Y deletions can be passed on to male offspring. It has further been suggested that other deletions may occur *de novo* in assisted conceptions, and there is some preliminary clinical evidence that expansion of existing Y chromosomal problems may occur hence creating a more severe phenotype in the subsequent generation [24].

Fetal Imprinting Disorders

Epigenetic imprinting is responsible for stable regulation of the possible expression patterns of an individual's genome. The most common modes of imprinting genes are via methylation, histone modification or DNA-binding proteins. Early in development, two distinct waves of imprinting (in the unfertilized egg and in the preimplantation embryo) wipe and then re-establish the correct epigenetic patterns for normally regulated development. Concern has arisen regarding the potential for disruption to the highly complex process of imprinting by ART techniques, particularly the techniques of superovulation and culture of the early embryo *in vitro*. Reports have suggested an excess incidence of the imprinted hypomethylation disorders Angelman and Beckwith-Weidermann syndrome following ART [25–27]. Whilst such disorders are very rare (with an estimated risk of Beckwith-Weidermann syndrome in pregnancies conceived using ART of <1 % [28]) and clearly do not affect the majority of fetuses arising from assisted conceptions, the concern regarding subtle epigenetic changes in the cultured embryo persists [29, 30]. Embryos cultured *in vitro* are exposed to a wide variety of stimuli that they do not encounter in unassisted conceptions including artificial culture media, temperature fluctuations and light exposure. All of these exposures have been suggested as potential

stimuli to subtly disrupt the normal patterns of methylation and other epigenetic patterns established during early development. Differences in DNA methylation patterns at various loci have been demonstrated in children conceived using ART [31], although this finding is inconsistent across studies [32]. In particular, the functional significance of variations in methylation patterns remains uncertain [33]. The developmental programming hypothesis postulates that a suboptimal early environment (for example culture *in vitro*) may have subtle but profound effects on long-term offspring health, and that these adverse effects could be mediated via epigenetic modulation [34, 35]. Furthermore, developmental programming effects can persist across generations [36], thus impacting not only on the later health of the current offspring, but also health outcomes in future generations. As the first children born using ART are currently in their mid-thirties and few have yet reproduced, there is no available evidence that could refute or support these concerns regarding health in later adulthood in human populations.

Clinical Practice Points

Where structural problems are seen the clinician should consider whether there might be subtle chromosome rearrangements as a contributory factor. Genetic advice may be taken and consideration given to micro-array testing if karyotyping is undertaken

Fetal Structural Anomalies

Collecting data to determine whether the rate of fetal structural anomalies is increased following ART is subject to a number of methodological complexities. The first is that the rate of spontaneous miscarriage may be higher in pregnancies conceived using ART, and hence the number of structural anomalies observed at term may be reduced. Conversely, couples that have conceived using ART may be less likely to undergo invasive testing (carrying a risk of miscarriage) or to terminate pregnancies where a structural anomaly is identified, hence inflating the rate of congenital structural anomalies observed at birth. This creates difficulty in designing an ideal study to determine the risk of structural anomalies. Collecting data at the time of birth risks missing a substantial proportion of anomalies in pregnancies that ended prior to birth, whereas collecting data at the time of detailed anomaly scans will not account for anomalies that are not detectable or were not detected on scan but were present at birth. The ideal study would therefore prospectively recruit pregnancies at the time of booking, collect detailed information on subfertility risks in the parents and include all structural anomalies observed both during fetal surveillance and at the time of delivery, regardless of ultimate pregnancy outcome. In the absence of such cohorts, retrospective analyses of anomalies that were present at delivery in neonates can still give important information.

Concerns regarding higher levels of fetal structural anomalies in pregnancies resulting from ART have most often been raised in the context of more invasive technologies, for example ICSI or blastomere sampling for pre-implantation genetic diagnosis. These techniques raised concerns that structural or biochemical damage to the ovum or early embryo would result in higher rates of congenital anomalies. The higher-than-expected incidence of monozygotic twin pregnancies arising from ART [37] suggests that there is some influence of *in vitro* micromanipulation on the structure of the early embryo. The true magnitude of the embryo-splitting effect in ART is masked by the number of dichorionic diamniotic twin pregnancies that are presumed to be dizygous following multiple embryo transfer; there is evidence, however, to suggest that a significant proportion of such pregnancies actually arise from a single conceptus [38, 39].

Numerous cohort studies have been performed to determine whether the incidence of fetal structural anomalies is higher in children following the use of ART (reviewed in [19]), including some more recent prospective cohorts [40]. Many of these studies have found a significantly increased rate of various structural problems [41–43], but the type and frequency found is not consistent across studies [44, 45]. Specific congenital malformations that have been found with a higher incidence in children conceived using ART include anorectal malformations [46], congenital cardiac lesions [40, 47, 48], nervous system [40, 49] and genital structural anomalies [40, 50]. One study has found subtle effects of conception via ART on cardiac morphology (including thickened ventricular walls and mild atrial dilatation) in the neonate that persist until at least 6 months of age, but the study was prevented from drawing robust conclusions by small sample size and inability to control for several potentially important confounding factors such as fetal growth restriction [48]. It has also been suggested that the rate of congenital abnormality is dependent on the technology utilized; some studies have found higher rates of structural abnormalities in children conceived following ICSI than after IVF [43, 51], although this is not consistently observed [52]. Several major meta-analyses have been performed to determine the rates across various populations, and conclude that the odds ratio of congenital structural anomalies is higher in any type of assisted conception than in spontaneously conceived pregnancy [52–54] with odds ratios ranging from 1.37 (95 % CI 1.26–1.48) to 2.01 (95 % CI 1.49–2.69). However, more recent work suggests that much of the excess risk of congenital abnormalities in pregnancies conceived using ART may be due to underlying infertility issues [50] rather than exposure to ART per se. A reworking of one of the largest meta-analyses thus far performed to assess congenital malformations in ART cohorts suggested that there was no statistically significantly increased risk of congenital anomalies after conception via ART when subfertility was adequately controlled for with an odds ratio of 1.01 (95 % CI 0.82–1.23) [55]. After adequate controlling for infertility and other parental factors, other studies have also concurred that there may be no increased risk of fetal structural anomalies with the use of IVF [56] and that the increased risk in such pregnancies may be attributable to underlying parental factors rather than the actual process of assisted conception. The chance of birth defects in spontaneously conceived pregnancies in women with a history of prior assisted-conception is higher than for those who have never previously required fertility treatment; OR 1.24, CI 1.01–1.56 [56].

Clinical Practice Points

All women in the UK are offered screening for structural anomalies at 18–20+6 weeks. No additional surveillance for structural problems is recommended

Fetal Growth

There is some evidence from cohort studies and meta-analyses that fetal growth may be reduced in pregnancies conceived using ART [3, 5, 9, 11, 57–60]. Most studies use low birth weight as evidence of intrauterine fetal growth restriction rather than serial scan measurements during gestation, although differences in fetal growth trajectory have been reported between different ART protocols [61]. Despite the high number of cohorts that have reported low birth weight associated with the use of ART, the relative contribution of underlying subfertility may account for more of the variation in birthweight than the technique used for conception [49, 62]. Importantly, a study that directly compared children conceived via ART with their spontaneously conceived siblings found no evidence of decreased birth weight in the ART group [63], hence many of the differences found on a whole population level may be attributable to intrinsic parental factors. Moreover, fetal growth restriction leading to low birth weight is more common in women diagnosed with subfertility regardless of mode of conception [64]. An increase in hypertensive diseases of pregnancy has also been observed in mothers who conceived after ART [60], which suggests a higher rate of placentation anomalies potentially leading indirectly to higher rates of fetal growth restriction.

Interestingly, several well-powered studies have observed a higher average birthweight in children conceived using ART who were the result of frozen embryo transfer rather than fresh [12, 17, 51, 65]. This finding is difficult to explain, but may relate to the baseline characteristics of parents who had surplus embryos to freeze after initial treatment, or to the fact that the intrauterine environment is less likely to be acutely influenced by hormonal stimuli [66]. The mechanisms by which mode of conception is linked to differences in fetal growth velocity remain to be fully established, but the increased birth-weights of children conceived after cryopreservation could point to a key role for the endometrial environment around implantation leading to better establishment of placentation.

It has been suggested that early *in vitro* culture of human embryos during ART can directly influence birth weight, regardless of other maternal and placental factors. One such study quasi-randomized embryos during the IVF process to culture in one of two commercially available media, and showed a difference in birth weight between the two groups [67]. While the imprinting of key growth genes such as IGF2 was not affected by method of conception, there were differences in other genes, including the regulator of pre-RNA processing small nuclear ribonucleoprotein peptide N (SNRPN) which may contribute to dysregulation of fetal growth [68]. Similar effects are noted in animal model of *in vitro* culture [69], where epigenetic differences in growth-related genes including IGF2 have been noted [70].

Clinical Practice Points

The RCOG guideline "Investigation and Management of the Small-for-gestational-age Fetus" (Green-top Guideline No. 31, revised January 2014) considers use of IVF as a minor risk factor for fetal growth restriction. Increased surveillance of fetal growth in the absence of other risk factors is not currently recommended.

Preterm Delivery

Many large and well-controlled cohorts have demonstrated an increase in the incidence of preterm delivery in pregnancies conceived using ART and this has been confirmed in several meta-analyses [4, 5, 9–11, 57, 60, 66, 71]. Some studies have estimated that the risk of any preterm birth is at least doubled in pregnancies conceived via ART compared to the spontaneously conceived population, with even higher odds of an early preterm birth [72]. This increase in the magnitude of risk is approximately the same in a mother with a history of prior preterm birth, making ART potentially a major risk factor for prematurity [72, 73]. Distinguishing retrospectively between spontaneous and iatrogenic preterm delivery is complex, but extremely important in determining the precise mechanism that could link mode of conception to gestation at delivery. Unfortunately there are few cohorts in which information specifically regarding the aetiology of the prematurity is available. There is evidence of both increased rates of preterm rupture of membranes and antepartum haemorrhage in pregnancies conceived using ART, either of which could potentially make substantial contributions to the rate of spontaneous preterm birth [60]. However, there is also evidence of increased incidence of maternal disease in pregnancies conceived using ART, particularly hypertensive disease, which could substantially increase the rate of iatrogenic preterm birth [11]. Iatrogenic preterm delivery rates may also be increased due to the increased propensity to placental abruption observed in association with conception using ART in several cohorts [13, 74]. However, no excess risk of preterm birth was found between sibling pairs conceived spontaneously and via ART, suggesting that in common with fetal growth, the propensity to preterm labour may be more associated with maternal factors than with exposure to ART per se [63]. In particular, a history of maternal subfertility, as assessed by time to conception, is independently associated with the risk of preterm birth [75].

In common with fetal growth restriction, the incidence of preterm birth among ART conceptions appears to be lower where embryo cryopreservation was used than in fresh cycles [17]. The decreased incidence of preterm birth may be linked to lower rates of antepartum haemorrhage in the cryopreservation group [66]. Furthermore, it may be the case that blastocyst rather than cleavage stage embryo replacement further increases the risk of a preterm or very preterm delivery [76]; however, more work is needed to disentangle the causative effect from potential confounding factors.

Clinical Practice Points

There is no current evidence to suggest that additional surveillance or testing would be of benefit in reducing the rates of preterm birth in pregnancies conceived using ART.

Stillbirth

Several large cohorts and meta-analyses demonstrate increased risks of perinatal death in pregnancies conceived using ART [4, 5, 11, 73]; however, the meta-analysis results are heavily influenced by a single case-control study from the US that showed a very high rate of perinatal death in the ART group [77]. When spontaneously and ART-conceived siblings pairs were studied the rates of perinatal death were comparable, and may have been reduced in the ART group. The issue of excess perinatal mortality rates in ART-conceived pregnancies is further complicated by the high rates of ART use in mothers who had previously experienced a perinatal death [63]. Perinatal deaths appear to be increased in women with a history of subfertility regardless of whether ART is utilized [78], making interpretation of the attributable risk of ART to perinatal death extremely complex. While perinatal death as whole may be increased by the use of ART, few studies are powered to look at normally formed singleton stillbirths. While there is some evidence that the stillbirth rate overall is increased in IVF pregnancies (OR 1.49 for IVF versus spontaneous conceptions) [9], the causal link is yet to be established.

Clinical Practice Points

Detection of fetal growth restriction can reduce stillbirth rates, therefore surveillance for growth restriction is recommended for pregnancies conceived using ART in the presence of additional risk factors.

Multiple Pregnancies

Much of the excess incidence of adverse perinatal outcome associated with ART has been attributed to the vast increase in multiple pregnancies associated with these techniques. In the US, the incidence of twin pregnancies increased by 100-fold since the widespread introduction of ART in the 1980s [79]. A considerable percentage of all multiple pregnancies in the US are the result of use of ART, despite international attempts to move towards more single embryo transfers [3]. Multiple pregnancy can be considered the most likely fetal complication of conception using ART.

Twin Pregnancies

While twin pregnancies in general are much more vulnerable to fetal complications than singleton pregnancies, conflicting data exist on whether the use of ART increases the risk of adverse outcomes above spontaneously conceived multiple pregnancies [80]. Some studies have found higher rates of adverse fetal outcomes after the use of ART, including risks of fetal structural anomalies [81], growth restriction [82], preterm birth [83, 84] and perinatal mortality [85]. However, in other studies, twin pregnancies conceived using ART have a comparable rate of major perinatal complications to those conceived spontaneously [86–88], and in some studies are even estimated to have a lower perinatal mortality rate [73]. The association between growth restriction and ART seen in singleton pregnancies does not appear to hold true in multiple pregnancies [58].

Chorionicity is a major factor in determining outcome in twin pregnancy, and while most twins resulting from ART are the result of double embryo transfer (and hence dichorionic and diamniotic), there is also a higher rate of monozygous twin pregnancy with ART compared to spontaneous conception, which cannot be circumvented using single embryo transfer [37]. Various explanations for this phenomenon have been suggested, including a direct effect of *in vitro* culture, higher likelihood of embryo manipulations, e.g., blastomere sampling for preimplantation genetic diagnosis [89]. It is well established that monozygotic twins are at higher risk of adverse perinatal outcomes (regardless of mode of conception) including prematurity, low birth weight, congenital anomalies [90] and perinatal death [90], compared to dizygous twins. In particular twins that are monoamniotic have additional risks, including cord entanglement [91]. There are case reports of conjoined twin pregnancies occurring after the use of ART, but there are insufficient data to judge whether the risk of this extremely rare outcome is substantially elevated [92]. Congenital anomalies in general do not appear to be more common in twins conceived using ART than in spontaneous conceptions [50], with the possible exceptions of neural tube defects [93] and anencephaly [81].

Higher-Order Multiples

The number of triplet pregnancies born to older mothers has increase fourfold in recent decades, primarily due to increased use of ART [94]. In 2007, 1.2 % of all deliveries following ART were of triplets. Such pregnancies may have significant adverse effects on maternal and neonatal outcomes [95, 96]. The relative rarity of spontaneous higher-order multiple pregnancies and the frequency of adverse outcomes [97–99] regardless of mode of conception limits the strength of the conclusions that can be drawn about the contribution of the ART process to fetal complications. The ability to draw conclusions regarding pregnancy outcomes is further complicated by the number of higher-order multiple pregnancies that subsequently undergo selective fetal reduction [100, 101]. There is limited evidence from studies of multiple pregnancies including both twins and triplets to suggest that

outcomes following ART conception are not worse than spontaneous conception [102, 103]. A recent study suggests that fetal outcomes of triplets conceived using ART may be improved by selective fetal reduction, particularly in terms of increasing birth weight and decreasing prematurity for no extra increase in pregnancy loss [98].

Clinical Practice Points

In the UK the National Institute for Health and Clinical Excellence (NICE) has produced guidelines for the management of multiple pregnancies. Management of ART assisted multiple pregnancies should be in line with the guidance.

Placental Complications

The increase in fetal complications from pregnancies resulting from ART may be in part attributable to increased placental complications, particularly fetal growth restriction, stillbirth and iatrogenic preterm delivery.

Vasa Praevia

Vasa praevia may be rapidly fatal to the fetus if bleeding occurs from the unprotected vessels traversing the membranes either with premature rupture of the membranes or during delivery. Over 50 % of neonates born following pregnancy complicated by vasa praevia require transfusion after delivery, and the perinatal death rate remains high [104]. Examination of placentas from both twin and singleton pregnancies conceived using ART has demonstrated a higher incidence of cord-insertion variants [105, 106], including vasa praevia [107, 108], and has estimated that the frequency of velamentous cord insertion in twins conceived via IVF may be as high as 10 % [109]. The reason for the increased incidence of vasa praevia in pregnancies conceived using ART remains uncertain, but it has been suggested that the normal process of blastocyst orientation at the time of implantation may be impaired by mechanical replacement of the embryo in the uterine cavity [109]. It has been further postulated that the increase in incidence of fetal growth restriction observed in pregnancies conceived using ART may be causally linked with abnormal cord insertion, although this hypothesis requires further verification [106]. The increased incidence of vasa praevia in IVF pregnancies, and its association with severe fetal complications has lead to the suggestion that specific screening of IVF pregnancies using transvaginal colour Doppler to detect vasa praevia should be undertaken [108]. Despite the low incidence of vasa praevia and the increasingly high proportion of pregnancies conceived using ART, transvaginal screening in IVF pregnancies may represent a cost-effective pregnancy intervention to prevent severe fetal morbidity [110].

Placenta Praevia/Accreta

Placenta praevia increases the risk of fetal complications during pregnancy, particularly with regard to antepartum haemorrhage, stillbirth and iatrogenic preterm delivery [111]. The overall incidence of clinically significant placenta praevia persisting until term is higher in ART-associated pregnancies than in those conceived spontaneously, with some studies suggesting an increase in risk as high as sixfold [9–11, 26, 59, 71, 112]. Some evidence exists that blastocyst transfer may be associated with higher rates of placenta praevia than cleavage-stage transfer [59]. When ART and spontaneously conceived pregnancies of the same mother were compared, the risk of placenta praevia still remained threefold higher in the ART group, implying that the increased risk is a direct effect of the ART process rather than a result of an underlying maternal structural complication such as Asherman's syndrome [113]. However, the increased risk is unlikely to result simply from low placement of the transferred blastocyst within the cavity, as the rates of placenta praevia are also elevated in pregnancies conceived using gamete intra-fallopian transfer (GIFT), where replacement occurs much higher in the maternal reproductive tract [13]. The incidence of both placenta praevia and associated antepartum haemorrhage may be reduced in pregnancies where cryopreservation rather than fresh transfer was used [112], which may relate to the fact that the endometrium is much less likely to have undergone stimulation prior to transfer in frozen cycles ("natural" cycles). More direct evidence that the unstimulated endometrium is less associated with placenta praevia comes from a large retrospective cohort Australian cohort, where the risk of placenta praevia was elevated fourfold in fresh cycles compared to "natural" unstimulated frozen cycles [114]. Importantly, this study was also able to include a group of women who had stimulated frozen cycles for comparison and in this group the incidence of placenta praevia was comparable to fresh cycles [114]. These findings strongly suggest that the stimulated endometrium may be the key risk factor for developing placenta praevia in this context, rather than the conceptus or underlying maternal factors. This finding correlates well with the risk of postpartum haemorrhage in pregnancies conceived using frozen cycle ART, which is lower in natural cycles than those using endometrial stimulation [13].

Placenta accreta has been observed at higher rates in pregnancies conceived using ART than in spontaneous pregnancies [115, 116], although this finding is not consistent across all cohorts [112]. The rarity of placenta accreta means that many studies are not sufficiently powered to assess invasive placentation as a separate outcome. It is remains uncertain whether the observed increase in placenta accreta in several studies may be due to intrinsic implantation dysregulation attributable to the ART process. Other possible explanations for the increased risk are maternal factors either linked to the requirement for ART (such as advanced maternal age) or linked to the underlying subfertility (such as previous endometrial resection [115]). In contrast with other fetal complications, the incidence of placenta accreta has recently been observed in a large Japanese cohort to be higher in ART cycles where cryopreservation was used than in fresh cycles [12].

Placental Insufficiency

The commonly observed phenotype of low birth weight in neonates born following the use of ART [3, 9, 12, 58, 59] has led to speculation regarding placental insufficiency in these pregnancies as a possible aetiological factor. Moreover, it has been observed that several key growth-related genes are up regulated in placental tissue from pregnancies conceived using IVF/ICSI techniques. These genes include H19 and PHLDA2, which are important mediators of intrauterine growth [61]. It is important to note, however, that no definite causal link to adverse fetal outcomes has been established.

Some studies have also suggested that the risk of early onset pre-eclampsia is higher in ART-conceived pregnancies [117], a relationship that persisted even after correction for possible aetiological factors including maternal age and pre-existing conditions [117]. This implies increased likelihood of a phenotype of insufficient trophoblast invasion; however, results from other studies are equivocal about the relationship between use of ART and development of early onset pre-eclampsia [59, 112].

Clinical Practice Points

In view of the increased risk of vasa praevia in ART-conceived pregnancies, if a low-lying placenta is seen at the time of routine fetal anomaly scanning, a transvaginal scan to look for vasa praevia should be undertaken.

Conclusions

There is evidence of an increased incidence of several important fetal complications in pregnancy following the use of ART [118]; however, it is important to note that the process of ART may not be the direct proximal cause of the observed adverse outcomes. Two potentially key aetiological factors are emerging from the developing body of literature on outcomes of pregnancies conceived using ART. Firstly, an increase in adverse outcomes is also seen in spontaneously conceived pregnancies of couples with subfertility [63] implying that the major under-lying factor behind the increase in fetal complications in pregnancies conceived using ART may be the underlying parental subfertility rather than an effect of the process of ART itself [71]. The second factor that may be an important determinant of pregnancy complications is stimulation of the endometrium. In particular, placenta-related complications are reduced in ‘natural’ cycles, where frozen embryos are replaced into an unstimulated uterine environment [13, 114]. The identification of endometrial stimulation as a factor increasing the risk of adverse fetal outcomes is especially important for the management of pregnancies conceived using ART as it is a modifiable risk factor and can be taken into account when designing optimal treatment

protocols. Regardless of the aetiology of the increased rates of fetal complications, the demonstrable increase in complication rates for these pregnancies naturally leads to the question of whether any routinely increased surveillance of these pregnancies is indicated and whether it could be of benefit in improving outcomes. The most beneficial intervention remains the avoidance of multiple pregnancy through the use of single embryo transfer where appropriate [80]. There is further evidence that routine transvaginal screening for vasa praevia may be cost-effective [110]. In view of the increase in perinatal mortality seen in the neonates of subfertile couples and the established links between subfertility, placental dysfunction and intrauterine growth restriction, serious consideration should be given to introducing routine third trimester monitoring of fetal growth via ultrasound for singleton pregnancies conceived using ART. For twin pregnancies, where increased surveillance is already in place during gestation, the increased risks of subfertility and ART are probably too subtle to justify any additional antenatal care needs [80]. Women who have conceived using ART should be made aware of a higher risk of induction of labour or Caesarean section [118], particularly with advancing maternal age.

Later-life outcomes for the children resulting from pregnancies conceived using ART are a matter of important debate, but are outside the scope of this chapter. Recent expert opinion based on systematic review implies that regardless of immediate fetal complication, there may be no long-term cognitive or developmental disadvantage to ART for the offspring [19]. This is highly reassuring, even in light of the evidence that suggests there may be an increase in fetal complications. However, we are still a long way from fully understanding these effects and from creating studies free of confounding to improve our understanding. Much more evidence is needed from well-designed prospective studies to disentangle causal effects contributing to fetal complications seen in association with conception using ART. Beyond this lies the requirement for more evidence regarding the mechanisms by which fetal complications might arise from the use of ART. Better understanding of the underlying mechanisms is vital in developing interventions to ameliorate these adverse effects.

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