In Vitro Fertilisation: Perinatal Risks and Early Childhood Outcomes

1. Background

Infertility is estimated to affect one in seven couples in the UK at some stage of their reproductive life. Nearly 40 years after the first assisted conception birth, in vitro fertilisation (IVF) is now a routine medical procedure and births following IVF account for just over 2% of all births in the UK. This is a lower proportion than in other European countries, possibly reflecting cultural differences, differences in public perception and the availability of public funding.

This paper summarises the evidence relating to outcomes of pregnancy, delivery and early childhood following conception by IVF and related procedures, and updates the previous Scientific Impact Paper published in 2012. Data concerning IVF and related procedures are reviewed, but not ovulation induction alone or with artificial insemination. Unless specifically stated, the term IVF is used to encompass IVF and any laboratory procedure associated with IVF. The main changes in practice since the last review are the increase in the proportion of transfers at the blastocyst rather than cleavage stage and the greater use of elective single embryo transfer (eSET). There is now robust evidence that live birth rates are increased following blastocyst stage transfer and up to two cycles of eSET produces similar live birth rates to a single double embryo transfer cycle while reducing greatly the chances of a multiple birth.

An increasing number of individuals are believed to travel outside the UK for treatment. Although, the extent of this is not possible to quantify, and because their treatment takes place elsewhere they are not included in figures published by the Human Fertilisation and Embryology Authority (HFEA).

Much of the available data are presented as relative risks and odds ratios. It is important to note that since most adverse pregnancy outcomes are rare, even when there is an increased relative risk associated with IVF, the absolute risk of these outcomes remains relatively low in many instances. Where comparative figures are provided, the results quoted are statistically significant unless indicated otherwise.

2. Perinatal outcomes

2.1 Multiple conceptions and multiple births

The single most influential determinant of both short- and long-term outcomes of pregnancy and birth is whether the pregnancy is a singleton or multiple gestation irrespective of whether conception is natural or assisted. The risks of adverse outcomes increase with the number of fetuses, zygostry and chorionicity, with monozygosity conferring the highest risk of potential miscarriage, major congenital anomalies, growth discrepancy and twin-to-twin transfusion syndrome. Compared with natural conception, IVF is associated with a two- to five-fold increased risk of monozygous twinning, although the absolute risk of monozygotic twins remains very low at between 0.9% and 2%. Blastocyst transfer increases the risk of monozygotic twinning (6%) compared with cleavage stage transfer (2%).

The most recent HFEA data confirm that multiple births following IVF in the UK have decreased from one in four IVF births in 2008 to one in six in 2013. This can be attributed to the HFEA multiple birth minimisation strategy, originally launched in 2001 and further strengthened in 2004, to
encourage eSET and limit the number of embryos transferred in women aged less than 40 years to two per cycle.

2.2 Preterm birth, low birth weight (LBW) and small for gestational age

Multiple pregnancy per se is a risk factor for preterm birth and its associated long-term consequences. This is one of the reasons that minimisation of multiple pregnancies in IVF is desirable. Additionally, there is an 8% increased risk of preterm birth (less than 37 weeks of gestation) with twins conceived through IVF compared with naturally conceived twins, and an 18% increase in the risk of very preterm birth (less than 32 weeks of gestation). For singletons, there is a 70% increased risk of preterm and a two-fold increased risk of very preterm birth associated with IVF. The relative contributions of spontaneous or elective preterm delivery following IVF is not known for either twins or singletons, although clearly each have largely different aetiologies principally reflecting infection and placental dysfunction, respectively. Maternal and treatment factors also impact outcome. For example, the use of donor oocytes more than doubles the odds of preterm birth. In addition, early fetal loss in a multiple gestation increases the risk of prematurity for the surviving singleton.

The risk of prematurity and LBW are intimately linked with multiple conception and birth. However, the independent effect of IVF on the increased risk of LBW (less than 2500 g) for multiple pregnancies is marginal at 1.04-fold and the increased risk of very LBW (less than 1500 g) is 1.13-fold. Whereas, the risk of LBW for IVF singletons is higher with a 1.61-fold increase and for very LBW there is a 2.12-fold increase. The fact that there is a 1.35-fold increased chance of being small for gestational age in singletons indicates that factors other than preterm birth also have an effect. One of these is the effect of a vanishing twin with a surviving singleton, the chances of which are mitigated with increasing use of eSET. However, the characteristics of the parents and type of treatment may also influence the risk of LBW and these are harder to address. While many of these risk factors cannot be modified, increasingly precise estimates of risk are available to improve counselling and increase the likelihood of couples choosing eSET.

2.3 Congenital anomalies

Around 5% of all infants are diagnosed with a congenital anomaly at birth or in early childhood. IVF is associated with a 30-50% increased risk of major congenital anomalies compared with natural conception, with similar results for both IVF and intracytoplasmic sperm injection (ICSI). This increased risk is not solely attributable to the increased risk of congenital anomalies associated with multiple births as this increase is also seen in singletons. The increased risk is, however, in part attributable to the underlying infertility, its determinants or associated factors, such as older parental age, those who have a prolonged time to conception, but nevertheless conceive naturally, also have an increased risk of having a baby with an anomaly, although the risk is not as high as for those who conceive following IVF. Importantly, the anomalies associated with IVF occur across the range of major organ systems, suggesting any causal effects are not necessarily timing dependent.

2.4 Vertical transmission of genetic diseases

Infertility may be partially genetic in origin, and with advances in assisted reproductive technologies (ARTs) potentially overcoming fertility obstacles, there has been concern of intergenerational transmission of disorders, resulting in an increased incidence of genetic abnormalities in children born as a result of fertility interventions. Overall, an increased prevalence of structural chromosomal anomalies in infertile men and women has been reported with a 4.6% prevalence of autosomal translocation and inversions in oligospermic men, and a 1.14% prevalence of autosomal reciprocal
balanced translocations in infertile women compared with 0.16% in the general population.\textsuperscript{16,17} However, transmission of chromosomal abnormalities can be prevented through the utilisation of pre-implantation genetic diagnosis (PGD) following karyotyping of men with azoospermia or severe oligospermia, and in women with a history of recurrent implantation failure or miscarriage (although the vast majority of cases will have a normal karyotype). Microdeletions of the long arm of the Y chromosome, in particular the azoospermia factor region, can also cause spermatogenic failure and either oligospermia or azoospermia, the latter preventing further vertical transmission.\textsuperscript{18,19} However, boys conceived from oligospermic men with Y chromosome microdeletions will inherit this subfertile phenotype, and further expansion or de novo deletions may occur, possibly resulting in a more pronounced phenotype in the offspring.\textsuperscript{20,21} In addition, other single gene disorders, such as cystic fibrosis, have been shown to be associated with infertility, which in the case of cystic fibrosis is due to congenital absence of the vas deferens. Vertical transmission of the common mutations can be avoided through partner testing and PGD technology if carrier status is confirmed. Nevertheless, carrier status may be passed on to the child.

There is increasing evidence that epigenetics may contribute to abnormal embryo and trophoblast development,\textsuperscript{22} subjects which are addressed in the Royal College of Obstetricians and Gynaecologists (RCOG) Scientific Impact Paper No. XX Epigenetics and Reproductive Medicine.\textsuperscript{23}

### 2.5 Perinatal mortality

Multiple births per se have a higher perinatal mortality rate (stillbirths and neonatal deaths combined) than singletons. Since IVF is associated with an increase in multiple births, overall IVF conception is thus associated with a higher perinatal mortality rate than natural conception adding to the desirability of eSET. However, the picture is more complicated when the comparison between outcomes for IVF versus natural conception is made separately for singletons and multiples. For singletons, IVF conception is associated with a 64% increased risk of perinatal death compared with naturally conceived singletons, although this is likely to be a minimum estimate since the relative risk estimates increase when data from only population-based, prospective cohort studies are considered and the effects of other forms of non-IVF infertility treatment are excluded.\textsuperscript{9} In the UK, for the singleton perinatal mortality rate in 2015, this equated to a rate following IVF of 9/1000 total birth compared with the general population rate of 5.6/1000. Although study findings are inconsistent overall, and despite evidence of an increase in pregnancy complications associated with adverse pregnancy outcomes, there is no evidence of a significant difference in perinatal mortality rates in multiple births conceived following IVF compared with natural conception (relative risk 1.04).\textsuperscript{8} This potentially reflects the lower incidence of monozygous twinning after IVF where the majority of IVF twins are due to the replacement of two or more embryos.

### 3. Specific IVF and related procedures

#### 3.1 Pre-implantation genetic diagnosis (PGD) and pre-implantation genetic screening (PGS)

PGD and PGS require the removal of one or more polar bodies, blastomeres or trophectoderm, from the embryo for genetic testing, in conjunction with ICSI to minimise the risk of contamination by residual sperm DNA.\textsuperscript{24} This allows for the transfer of embryos free of monogenetic diseases and aneuploidy. Despite the removal of a variable amount of material from the developing embryo, the overall prospect for the child appears in line with standard ICSI,\textsuperscript{25,26} with no differences seen in gestational age at birth, birth weight, perinatal death or major anomalies.\textsuperscript{24} The perinatal death rate for singletons born following PGD was 12/1000 births compared with 19/1000 following singletons born after ICSI alone ($P = 0.26$).\textsuperscript{24} The major anomaly rate for children born after PGD was 2.3% compared to 2.7% for children born after ICSI ($P = 0.69$).\textsuperscript{24} No difference has been identified in
antenatal complications, such as hypertension and diabetes. Furthermore, no difference in perinatal deaths was seen for multiple births conceived after PGD or ICSI (81 versus 52 per 1000 births; P = 0.11).

Notably, all of these perinatal mortality rates are substantially higher than for the general population, which in the UK in 2014 were 5.5/1000 and 18.8/1000 total births for singletons and twins, respectively; further research is required to elucidate the time of death to determine whether timing of induction of labour could be used to minimise the risk of perinatal death at term.

Adverse pregnancy outcomes have not been shown to be specifically attributable to PGD, with no differences seen between the techniques employed, but highlights infertility as an independent risk factor.

In the early stages of development, a new concept, expanding the field of PGD/PGS, has been postulated regarding the significant role of mitochondrial DNA quantity as a biomarker in implantation potential and the development of chromosomally normal embryos. Mitochondrial DNA levels have been found to be higher in embryos from older women and those with a lower implantation potential despite being euploid or with aneuploidy. This could form the basis of a less expensive, reproducible clinical technique, with overall improved outcomes.

3.2 Blastocyst culture

The extended culture of embryos in vitro from the traditional cleavage stage (days 2 or 3) to the blastocyst stage (days 5 or 6) has seen an exponential increase in use in recent years, as a means of improving embryo selection, and uterine and embryonic synchronicity, and subsequently, pregnancy rates with an increased uptake of eSET. The embryo is sequentially cultured in different media to facilitate in vitro development. However, extended culture may cause genetic changes in the trophodermal cells leading to abnormal placentation and implantation, potentially explaining some of the adverse effects seen with extended blastocyst cultures.

A Cochrane review reported a significant increase in live birth rate after blastocyst stage transfer compared with cleavage stage transfer (38.8% versus 31%, respectively). This was confirmed by a systematic review and meta-analysis which demonstrated that the probability of live birth after fresh IVF cycles is 40% higher after a blastocyst stage embryo transfer compared with a cleavage stage embryo transfer, when equal numbers of embryos are transferred. However, after adjusting for confounding factors, the risk of preterm birth among singletons is 32–35% greater after a blastocyst stage transfer than after a cleavage stage transfer. Furthermore, a 30% higher incidence of male fetuses has been observed with blastocyst stage embryo transfers, possibly due to more rapid development of male embryos compared with female embryos. This gender predominance has also been noted for preterm deliveries and attributed to a greater synthesis of active prostaglandins in the placenta of male fetuses.

Birth weight is influenced by a number of factors, including the characteristics of the woman and environmental factors. The stage of embryo transfer also plays a role, with blastocyst stage transfer more likely to result in large for gestational age babies, with an average birth weight difference of 146 g. This may be partly attributed to the culture media used. Studies conducted in animal models have confirmed some of these findings and raised some concerns about potential deleterious effects of extended embryo culture (see above), including imprinting disorders, behavioural abnormalities, and cardiovascular and metabolic dysfunction.
In a meta-analysis, the risk of congenital anomalies was 30% higher for infants born as a result of a blastocyst stage transfer compared with cleavage stage transfer, although the types of anomalies were not reported. This effect may be partly attributable to an increase in monozygotic twinning, although the evidence regarding blastocyst transfer and monozygotic twinning is conflicting. Time lapse monitoring semi-quantitatively evaluates the morphology and kinetics of the developing embryos, enabling earlier selection of those with a higher implantation potential and the avoidance of epigenetic disorders that can occur with extended culture. Nevertheless, the potential risks associated with the extended culture period requires continued surveillance of the children born as a result of blastocyst stage embryo transfer.

3.3 Assisted hatching (AH)

AH is a technique whereby the zona pellucida is disrupted to facilitate implantation. Recent data, confirmed in a Cochrane review, continues to show enhanced clinical pregnancy rates, but no increase in the live birth rate following AH. Furthermore, the procedure itself can have detrimental effects outside of the IVF process, including irreversible damage to the embryos and an increased risk of multiple order pregnancies with their associated morbidities, although there is insufficient evidence to conclude that AH is specifically associated with an increased monozygotic twin pregnancy rate. The long-term impact of AH on the pregnancy and the resulting children is unknown.

3.4 In vitro maturation (IVM)

IVM was developed to avoid the adverse effects associated with gonadotropin administration. The technique involves immature oocytes being retrieved from unstimulated ovaries and subsequently matured in vitro. Although based on relatively small numbers, the evidence suggests that pregnancy rates are overall lower in IVM cycles compared with those incorporating controlled ovarian stimulation. Data from a small retrospective case–control study suggested live birth rates in the order of 16.5% versus 44.3% respectively, with ovarian hyperstimulation syndrome occurring in 8.2% of cases in the controlled ovarian stimulation group and none being reported in the IVM group (0%). Cost and time are additional benefits that have been noted for IVM.

IVM has now been extended to treat women wishing to undergo fertility preservation prior to imminent gonadotoxic therapy, and in those where ovarian hormonal stimulation is contraindicated.

However, the process of IVM is not without potential complications for the resulting children. IVM may alter normal oocyte maturation, with modifications seen in normal genetic and cytoplasmic integrity, theoretically increasing the incidence of imprinting disorders. Over 2500 babies have been born worldwide following IVM, and although formal prospective paediatric follow-up studies are limited and overall numbers are low, similar obstetric outcomes and congenital anomaly rates between babies born following IVM, IVF and ICSI have been reported. Neurological development of children, born following IVM, at 2 years of age appeared to be normal, although this conclusion is based on two very small case series.

3.5 Cryopreservation

Cryopreservation techniques have progressed rapidly from slow freezing to vitrification with clinical pregnancy and live birth rates being comparable to the transfer of fresh embryos. Embryo
cryopreservation has gained increasing importance over the years, helping to drive forward the eSET policy to minimise the multiple pregnancy rate.50

Data from available studies have suggested similar gestational ages at birth following the transfer of fresh, slow frozen or vitrified embryos, with the risk of LBW babies, small for gestational age and preterm deliveries being higher for fresh cycles.49 Furthermore, controlling for contributory factors, such as parental characteristics, babies born after the transfer of frozen embryos tend to be larger for dates than those born after fresh transfer cycles,49,51 irrespective of maternal factors; and there is no difference in the congenital anomaly rate between fresh and frozen transfer cycles.50 A Danish register study50 found no difference between the incidence of cerebral palsy, intellectual disability, imprinting diseases or malignancies in children conceived after frozen replacement cycles and children conceived after fresh cycles or naturally conceived children. However, a doubling in perinatal mortality rates was found in children born from cryopreserved embryos (16/1000 births) compared with naturally conceived children (8/1000 births). Of note, the perinatal mortality rate following fresh treatment cycles was 14/1000 births.

One study suggested that children conceived after a frozen embryo transfer who were delivered at term had a greater number of visits to hospital in the early neonatal period, most commonly with respiratory conditions, but an overall shorter time spent in hospital compared with children born following fresh transfer cycles.51

Vitrification has also been extended to include the cryopreservation of oocytes for fertility preservation prior to gonadotoxic therapy or for social reasons.52 When compared with fresh oocytes vitrification does not increase the risk of obstetric complications (such as diabetes- or pregnancy-induced hypertension), does not adversely affect fetal development (birth weight, anomalies) or increase perinatal risk.52

Data on long-term outcomes are sparse and long-term studies of children born after the vitrification of embryos or gametes are needed, because of the potential cytotoxic effects of the cryoprotectants used and the contamination associated with contact with the liquid nitrogen.49,52

4. Long-term outcomes for children

The physical, neurological and developmental health of children born following IVF is one of the most important aspects when discussing the potential adverse effects of treatment and is an area receiving increased scientific attention. Overall, the neuromotor, cognitive, language and behavioural outcomes of children born following IVF appear similar to those born following a natural conception.53–55 Of particular interest has been the risk of autism spectrum disorders in children born following IVF, but the findings so far suggest that there is no excess risk and observed differences may be because of confounding effects of socioeconomic circumstances.56,57 However, there remains a two-fold increased risk of cerebral palsy following IVF,58,59 which is partly, but not wholly, explained by the higher rates of preterm delivery and multiple births following IVF conception.

It is reassuring that large registry-based studies have all reported no increased risk of cancer overall among children born after IVF, and although individual studies find small increases in specific cancers, no consistent pattern has emerged.60–62 A growing number of studies have also suggested a higher prevalence of asthma among children born after ART,63–65 but not of atopy or allergy.

Researchers are now exploring the more subtle effects of IVF on longer term health outcomes, with a focus on growth, adiposity and cardiometabolic profiles. The Barker hypothesis predicts that
adverse antenatal conditions can lead to adverse consequences for the adult; this raises the question of whether there is an associated link between those children born following IVF who experience cardiometabolic disturbances during adolescence and adulthood. In general, little impact has been observed on the height, weight or BMI of children born following IVF.\textsuperscript{66,67} However, effects have been observed on growth trajectories: for example, children born following IVF may show early catch-up growth,\textsuperscript{68,69} and culture medium may influence both birthweight and early childhood weight gain.\textsuperscript{70} Higher peripheral adipose tissue mass has been observed in IVF children, and higher blood pressure and increased fasting glucose have also been reported.\textsuperscript{71,72} These findings need to be confirmed and the longer term implications of such differences require further investigation, with larger metabolic epidemiological studies of adolescents and adults who were born following IVF.

It has been hypothesised that boys born after ICSI owing to severe male factor infertility may be more likely to experience fertility problems themselves, although such effects may relate to IVF treatment for specific parental fertility disorder (see section 2.4). Small studies to date have shown no effect on testicular development as indicated by serum inhibin B level.\textsuperscript{73} Pubertal timing appears normal among children born after fertility treatment,\textsuperscript{74} but there is currently little evidence regarding their future fertility.

5. Risks associated with parental factors

5.1 Maternal and paternal

Increasing maternal age is a risk factor for almost all pregnancy and perinatal complications. The average age at which women attempt to conceive continues to rise; consequently, IVF is increasingly carried out in older women who will have a predisposition to pregnancy complications. However, comparison with age-matched controls has shown an increased risk of complications associated with infertility, with a higher rate of caesarean section delivery, obstetric haemorrhage, pre-eclampsia, pregnancy-induced hypertension and gestational diabetes in the older age group.\textsuperscript{75,76} These conditions are associated with poorer perinatal outcomes for the neonate, including congenital abnormalities, preterm delivery and LBW, and admission to the neonatal intensive care unit. By virtue of their age, older women are more likely to have pre-existing comorbidities further complicating their pregnancy course and outcome. Importantly, women with significant comorbidities, regardless of their age, should receive pre-IVF assessment and counselling focusing on the risks for themselves and their pregnancy associated with their existing diseases.

Until recently, less focus has been placed on the impact of advanced paternal age on fecundity and reproductive outcomes. Advanced paternal age is associated with poorer spermatozoa parameters, including reduced motility and morphology, increased incidence of genetic abnormalities (such as achondroplasia)\textsuperscript{77} and pregnancy loss, further compounding the effects of advanced maternal age\textsuperscript{78} and obstetric complications, including pre-eclampsia, preterm birth and LBW.\textsuperscript{77} Advanced paternal age has also been found to be associated with several malignancies (such as leukaemia) and psychiatric morbidity (such as autism spectrum disorders, schizophrenia and bipolar disorders).\textsuperscript{77,78} The limiting factor in terms of counselling is that there is currently no consensus on a defined threshold above which the paternal age is considered advanced.\textsuperscript{77,78}

5.2 Recipients of donor oocytes

Treatment with donor gametes has become increasingly acceptable over the past decade. There appears to be an increase in early pregnancy, adverse obstetric and perinatal complications associated with donor gamete treatment. In particular, there is an increased risk of pregnancy-induced hypertension ranging from 16% to 40%, impaired placentation, and pre-eclampsia (2.1 to
3.3 increased risk) with the highest risk observed in primiparous women,\textsuperscript{79-82} even taking account of the age of the recipient and the ART used.\textsuperscript{81} A meta-analysis\textsuperscript{83} of the evidence suggests that neonates conceived following the use of donated oocytes are 18% more likely to be LBW (less than 2500 g) compared with neonates conceived from autologous oocytes, although the risk is reduced when the pregnancy nears term. There is also a 75% greater risk of preterm birth.\textsuperscript{80} The overall poorer outcomes for neonates conceived from donor oocytes in contrast to autologous oocytes remained when controlled for multiple births.\textsuperscript{80,83} In contrast, there is a trend towards a lower incidence of congenital anomalies in donated oocyte conceived neonates,\textsuperscript{83} most likely related to the younger age of the donor. Donor–recipient cycles pose a number of ethical and long-term health implications, with larger studies needed to guide reproductive counselling.

5.3 Reproductive disorders
Reproductive disorders encompass a wide variety of conditions, including endometriosis, adenomyosis, polycystic ovary syndrome and uterine fibroids, that have been associated with adverse obstetric outcomes through common hormonal dysfunction and increased inflammatory states. These conditions have been implicated in disorders of poor placenta, with the associated increased risk of preterm birth, fetal growth restriction and hypertensive disorders.\textsuperscript{84} They can occur independently or in combination, and may concurrently be associated with subfertility. The poor obstetric and neonatal outcomes may, therefore, be attributable to the combined effect of IVF treatment and older maternal age.\textsuperscript{84}

6. The role of the subfertile phenotype
The potential impact of underlying parental subfertility adds complexity to the study of health outcomes for children born following IVF. It is increasingly clear that factors which predispose to infertility are also linked to adverse perinatal outcomes, with subfertility acting as a proxy for this. Children born after fertility treatment may experience the double health impact of subfertility and of subsequent treatment. Many epidemiological studies compare babies born following IVF to those born after any natural conception, so that the comparison group contains a wide range of time to conception – including couples who would fulfil the definition of ‘infertile’ and would have been eligible for ART – and is therefore not comparing ‘infertile’ to ‘fertile’. To assess the effect of treatment, over that of underlying infertility, some studies have compared outcomes following IVF with children born to a subfertile group, defined as a prolonged time to natural conception. Analyses of this type suggest that cerebral palsy, for example, is associated with treatment but not time to conception,\textsuperscript{85} and therefore further work to determine the separate effects of parental subfertility and treatment is warranted.

7. Opinion
- The collective evidence suggests that the increased risk of obstetric complications, congenital anomalies and other adverse outcomes in births following IVF can be attributed largely, although not wholly, to inherent parental characteristics, as well as the occurrence of multiple order pregnancies.
- ARTs contribute to epigenetic changes throughout the genome of the gametes and resultant embryos.
- Many of the adverse outcomes described in this paper are relatively rare and even where risks associated with IVF treatment are increased, the outcomes remain uncommon.
• Not all outcomes occur in isolation and the long-term effects of some aspects, including epigenetic changes, are as yet unknown.
• Having conceived following infertility treatment, parents are likely to wish to normalise their pregnancy experience; nevertheless, it is prudent to consider these pregnancies as potentially high risk on a woman by woman basis, not least because the woman is likely to be older, to have pre-existing comorbidities and, consequently, be more prone to pregnancy complications and adverse outcomes.

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All RCOG guidance developers are asked to declare any conflicts of interest. A statement summarising any conflicts of interest for this Scientific Impact Paper is available from: https://www.rcog.org.uk/en/guidelines-research-services/guidelines/sip08/

The final version is the responsibility of the Scientific Advisory Committee of the RCOG.

The paper will be considered for update 3 years after publication, with an intermediate assessment of the need to update 2 years after publication.

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