DOI: 10.1111/tog.12504
The Obstetrician & Gynaecologist
http://onlinetog.org
2018;20:177–186

Complications of assisted reproductive technology treatment and the factors influencing reproductive outcome

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Accepted on 1 February 2018. Published Online 21 June 2018.

Key content

- Ovarian hyperstimulation syndrome and multiple pregnancy risks are the two key complications of assisted reproductive technology (ART) treatment.
- There appears to be no direct association between ART treatment and an increased risk of invasive cancer in infertile women, but there may be a small increased risk of borderline ovarian tumours.
- There is suggestive, yet unconvincing, evidence that ART treatment may increase several risks, including childhood cancer risk to children.
- A slight increase in the risk of some adverse perinatal outcomes following ART treatment may be caused by the underlying fertility problem.
- Female age, ovarian reserve markers and previous obstetric history are the best predictors of ART success.
- Currently, there is insufficient evidence to recommend the routine use of some of the interventions to improve reproductive outcome.

Learning objectives

- To have an overview of different iatrogenic complications for women undergoing ART and the child or children born following ART treatment.
- To understand the evidence-based synopsis of factors affecting ART success.
- To appreciate the limited or conflicting nature of available evidence for certain interventions used to maximise ART treatment outcome.

Ethical issues

- Should ART treatment be offered to older women?
- What are the long-term safety implications of some of the 'adjuvants' used to improve ART success?

Keywords: assisted reproductive technology / cancer risk / interventions / multiple pregnancy / ovarian hyperstimulation syndrome

Please cite this paper as: Bhandari HM, Choudhary MK, Stewart JA. Complications of assisted reproductive technology treatment and the factors influencing reproductive outcome. *The Obstetrician & Gynaecologist* 2018;20:177–186. https://doi.org/10.1111/tog.12504

Introduction

The use of assisted reproductive technology (ART) is established as an efficacious and relatively safe procedure for people with fertility problems wishing to achieve pregnancy. The number of ART cycles is increasing worldwide and the number of babies born from ART has increased significantly since the 1980s. Like any other medical treatment or surgical procedure, ART carries certain risks, some associated with the treatment and the others associated with the outcome (Table 1). The first part of this review discusses different iatrogenic complications of ART affecting the potential mother and child, which remain major challenges to practitioners providing fertility care.

ART success rates vary significantly between assisted conception units, which are constantly making efforts to improve reproductive outcomes. For people who choose to undertake ART treatment, a negative treatment outcome may have devastating effects, emotionally, psychologically and – at times – financially. The reasons for an unsuccessful outcome may be embryological, endometrial or endocrinological, but in the majority of cases they are unclear. The second part of this review aims to provide evidence-based information about the factors affecting ART success (Table 2).

Complications of assisted reproductive technology

Ovarian hyperstimulation syndrome

Ovarian hyperstimulation syndrome (OHSS) is an iatrogenic adverse effect of the exogenous administration of gonadotropin for controlled ovarian stimulation (COS) in

Table 1. Complications of assisted reproductive technology treatment

Associated with treatment	**Woman** Side-effects of drugs Ovarian hyperstimulation syndrome Risks associated with sedation or anaesthetic Risks associated with oocyte retrieval – haemorrhage and infection Surgical sperm recovery risks – infection, bleeding, testicular atrophy
Associated with outcome	**Woman** Multiple pregnancy Ectopic pregnancy and heterotropic pregnancy **Children** Congenital anomalies in children
Further evidence is required	**Woman** Borderline ovarian tumour **Children** Childhood cancer risk Imprinting disorders

ART treatments. Administering human chorionic gonadotropin (hCG) for final follicular maturation, or the endogenous hCG produced as a result of pregnancy, increases the risk of OHSS in susceptible individuals. Younger age, low body mass index, polycystic ovary syndrome and a history of OHSS all increase the risk of OHSS. Increased capillary permeability mediated by endocrine factors (activation of follicular renin-angiotensin system) and vasoactive cytokines (vascular endothelial growth factors) is thought to be responsible for the resulting hypovolaemia and for the characteristic fluid accumulation in the third space.[1] Early OHSS occurs soon after oocyte retrieval and is a result of exogenous hCG administered for final follicular maturation on a background of excessive ovarian response to follicle-stimulating hormone. Late OHSS occurs 10 or more days after the hCG trigger and is generally precipitated by the effect of endogenous hCG from an early pregnancy.

Mild OHSS is a complication reported in up to one-third of the women undergoing ART treatment. The severe form of OHSS is reported in 1–2% of ART cycles.[1] Commonly reported symptoms of OHSS are abdominal distension and pain, nausea, vomiting, shortness of breath and subjective low urine output. Although a self-limiting condition, it may worsen and be accompanied by ascites, pleural and pericardial effusions, renal dysfunction and, sometimes, abnormal liver function test results. Recognised complications of OHSS are renal failure, venous and arterial thromboembolism, adult respiratory distress syndrome, haemorrhage from ovarian rupture and, very rarely, death.[1]

Monitoring for progression of OHSS should include daily measurements of weight, abdominal girth and fluid intake and output, and blood tests for full blood count, electrolytes, liver and renal function.[2] Additional investigations including pelvic, abdominal and chest ultrasound, electrocardiography, blood gases and chest X-ray should be undertaken as indicated by clinical features. Supportive therapy for symptoms including analgesics (avoid non-steroidal anti-inflammatory drugs), anti-emetics, careful fluid replacement (preferably oral, but intravenous if not tolerated orally), drainage of ascites and thromboprophylaxis should be initiated.[2] Mild to moderate OHSS can be managed on an outpatient basis and spontaneous resolution of symptoms is

Table 2. Factors affecting treatment outcomes of assisted reproductive technology (ART)

Factor	Effect
Female age	Age-related decline in fertility and ART success
Previous obstetric history	Previous pregnancy and live birth increases the odds of successful ART treatment
Maternal body mass index (>30)	Conflicting evidence of ART outcome Increased obstetric and perinatal risks
Lifestyle measures	Excessive alcohol, smoking and caffeine have negative influence on ART outcome
Ovarian reserve markers	Anti-müllerian hormone and antral follicle count can accurately predict hypo or hyper ovarian response to controlled ovarian stimulation
Number of oocytes retrieved	Live birth rate increases with increasing number of oocytes retrieved up to 15 and declines beyond 20 oocytes
Fertilisation method	The routine use of intracytoplasmic sperm injection for non-male factor infertility has shown no significant advantage over in vitro fertilisation
Embryo quality	Better embryo quality is associated with higher chances of pregnancy Blastocyst transfer improves live birth rate
Number of embryos transferred	Double embryo transfer leads to a higher live birth rate, but significantly higher multiple birth rate
Male factors	Direct relationship between semen quality and ART outcome No relationship between anti-sperm antibodies and ART outcome Sperm function tests have no role in routine clinical practice

expected in 7–10 days. Patients with severe OHSS and those with significant pain or nausea that limits oral intake are usually managed as inpatients and more severe cases (critical OHSS) are admitted to an intensive care unit for management under a multidisciplinary team.[2]

Multiple pregnancy

The essential aim of ART is the birth of a single healthy child. Multiple pregnancy, which carries an increased risk for the woman and her babies, is the single biggest adverse effect of ART treatment. The chance of a multiple pregnancy is almost 20 times higher with ART treatment than with spontaneous conception. Multiple pregnancies carry much higher obstetric risks for women: the risk of miscarriage, pre-eclampsia, gestational diabetes, haemorrhage and instrumental delivery are all higher for women with multiple pregnancy. The risk of babies being born prematurely, being small for gestational age (SGA) and having low birthweight (LBW) is higher for twins, who often require hospitalisation for significant periods of time. Multiple pregnancy is also linked to an increased risk of perinatal mortality of one or both twins, and carries a risk of long-term health and cognitive effects.

Data from the Human Fertilisation and Embryology Authority (HFEA) report from 2006 suggest a staggering multiple birth rate of 24%.[3] However, a combination of elective single embryo transfer (eSET) policy, and the conviction of clinicians and embryologists that eSET is in women's best interests, is responsible for a decline in multiple pregnancy rates.

The chance of a woman becoming pregnant with monozygotic (identical) twins, including monochorionic monoamniotic twins, appears to be higher following eSET (0.7–3.1%) than in natural conceptions (0.4%).[4] Blastocyst transfer and intracytoplasmic sperm injection (ICSI) are associated with an increased incidence of monozygotic twins following eSET compared to cleavage stage embryo transfer (ET) and in vitro fertilisation (IVF), respectively.[5]

Elective single embryo transfer strategy

Traditionally, most women undergoing ART treatment had multiple embryos transferred to maximise their chances of becoming pregnant. As a result, there was a high rate of multiple pregnancies, which resulted in poorer clinical outcomes for both the mother and her babies. Recognising this as a significant public health burden, the HFEA, in conjunction with professional organisations and patient groups, produced a policy[3] requiring UK fertility clinics to adopt their own 'multiple births minimisation strategy' to suit their practices and patients. The overall aim of this policy was to reduce the national multiple birth rate to meet the HFEA target of 10%. Since the policy was introduced in January 2009, clinics have increased their efforts to identify more women who might be suitable for eSET as opposed to multiple embryo transfer. As a result, the number of women having eSET has greatly increased from less than 5% in 2008 to 28.7% in 2014. This has had a significant impact on minimising multiple birth rates without affecting live-birth rates (LBRs) (Figure 1).[6]

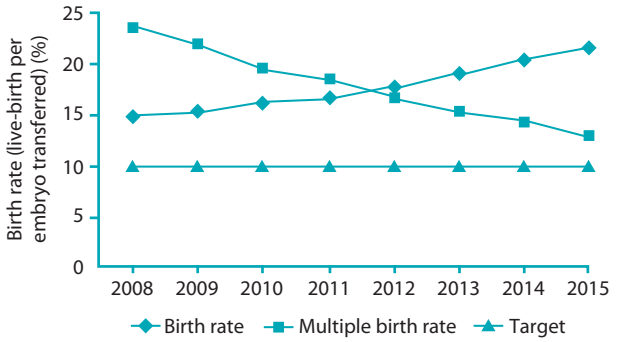

Figure 1. Birth rates and multiple birth rates between 2008 and 2015. The Human Fertilisation and Embryology Authority data shows birth rates and multiple birth rates since the introduction of the Multiple Births Minimisation Strategy. The birth rate (live-birth per embryo transferred) has steadily increased from just under 15% in 2008 to 21.6% in 2015 and the elective single embryo transfer strategy has reduced the multiple birth rate per IVF cycle from 24% in 2008 to 13% in 2015. The target is to reduce the multiple birth rate per IVF cycle to 10%.[3,6]

Ectopic pregnancy and heterotopic pregnancy

The risk of ectopic pregnancy and heterotopic pregnancy (ectopic pregnancy along with an intrauterine pregnancy) is noted to increase following ART treatment. The prevalence of ectopic pregnancy in women undergoing ART treatment ranges between 2.1 and 8.6% (background risk of 1–2% following natural conception). The incidence of heterotopic pregnancy is 1 in 30 000 in the general population, which increases to 8 in 1000 following ART treatment.[7] Maternal risk factors such as cigarette smoking, previous pelvic inflammatory disease, endometriosis, previous ectopic pregnancy and previous tubal surgery impair tubal function and increase the risk of ectopic pregnancy both in natural conceptions and in ART cycles. ART-related factors may also increase the risk of ectopic pregnancy, for example, through the loss of normal biological interactions between the endometrium, fallopian tube and embryo caused by alterations in the hormonal micro-environment following COS as well as embryo quality, multiple embryo transfer, embryo transfer techniques (which may influence reverse migration of embryos from the uterine cavity) and embryo transfer stage.[7]

Complications of the oocyte retrieval procedure

Transvaginal oocyte retrieval (TVOR) is a relatively safe procedure, but observational studies report it to be associated

with complications of minor vaginal bleeding (1.4–18.4%), pelvic infection (0.1–0.6%) and, rarely, with severe intra-abdominal bleeding (0.05–0.2%).[8] Though the quoted figures are very small, these complications can cause significant maternal morbidity, thus it is vital to minimise these risks. However, a global survey revealed wide variations in the ways that at-risk women are identified in clinical practice and the measures taken to minimise excessive bleeding and infective complications during TVOR.[8]

Cancer risk

For women undergoing ART treatment, concerns have been raised regarding COS-related supra-physiological concentrations of gonadal sex hormone secretion promoting the growth of hormone-dependent tumours such as in the breast, ovary and endometrium later in life (Table 3). Although in vitro studies have demonstrated possible direct tumorigenic effects of gonadotropins,[9] the clinical evidence demonstrating a precise relationship between ART and cancer in women undergoing ART treatment remains patchy, weak and contentious. Many published studies do not take confounding factors such as age, genetic predisposition and underlying infertility into account.

Pooled evidence from observational studies suggests that COS does not predispose women to an increased risk of non-hormone-dependant cervical cancer.[10] Breast cancer is associated with reproductive history and with endogenous or exogenous hormonal factors. A meta-analysis has suggested that the risk of breast cancer is no higher in women who have had fertility treatment than the general population.[11] A study conducted in 2012 found no increased risk of breast cancer in women undergoing ART treatment, but the age-related findings from this study suggest a possible greater risk of breast cancer in women younger than 25 years of age.[12]

The risk of ovarian cancer following ART treatment has been greatly debated. A systematic review and meta-analysis conducted in 2013 found a significantly higher risk of ovarian and endometrial cancer in women following ART treatment than in the general population (pooled effect estimates of 1.50, 95% confidence interval [CI] 1.17–1.92 and 2.04, 95% CI 1.22–3.43, respectively).[10] However, when the confounding factor of infertility was adjusted, there was no significantly increased risk (pooled effect estimates of 1.26, 95% CI 0.62–2.55, and 0.45, 95% CI 0.18–1.14, respectively). A large study published in 2015, which conducted extensive record review and linkage analysis, found a higher risk of ovarian cancer in women who were younger when starting ART treatment, with fewer live births and with female factor infertility, particularly endometriosis. However, no increased risk was noted in women who underwent ART treatment for non-female factor infertility.[13] A large Dutch cohort of subfertile women found a significantly higher overall risk of borderline ovarian tumours in women following ART treatment compared to those who did not have ART treatment (hazard ratio [HR] 6.38, 95% CI 2.05–19.84).[14]

The National Institute for Health and Care Excellence (NICE) recommends that clinicians should advise women undergoing ART treatment that there is no direct association between ART and an increased risk of invasive cancer; however, with the available evidence, it is difficult to exclude a small increased risk of borderline ovarian tumours.[15] It is possible that ART is not the cause, but that there may be an inherent increased risk of developing ovarian cancer in infertile women.

Table 3. Assisted reproductive technology and cancer risk in women[10–15]

Type of cancer	Change in risk
Cervical cancer	No increased risk
Breast cancer	No overall increased risk Possible small increased risk in women under 25 years of age
Ovarian cancer	No increased risk for non-female factor infertility Possible increased risk of Borderline ovarian tumour
Endometrial cancer	No increased risk

Early menopause

Since COS allows increased follicular recruitment and oocyte harvest, some concerns have been raised about a theoretical increased risk of premature follicle depletion and early menopause in women undergoing ART treatment. A questionnaire-based retrospective study found no significant association between the number of ART cycles or pregnancies and menopause.[16] This is because follicles recruited after COS are selected from the pool of follicles that would have generally undergone atresia in a natural cycle and that the effects of COS are not on the primordial follicles.

Perinatal outcomes

It has become clear that adverse perinatal outcomes such as preterm delivery, LBW, SGA, perinatal mortality and admission to neonatal unit are higher in ART-conceived babies than in naturally conceived babies.[17–19] This was thought to be attributed to a higher incidence of multiple pregnancies, but there appear to be increased adverse perinatal outcomes even for singletons born following ART treatment.

A population-based study showed that singleton pregnancies following ART treatment were associated with LBW, shorter duration of pregnancy, and increased risk of SGA and perinatal mortality compared to the spontaneously conceived singleton babies to the same (subfertile) mother.[20] However, in the same study, the authors found the differences between spontaneous and ART conceptions to be smaller and

were no longer significant in sibling relationship comparisons, suggesting the possible causal role of subfertility in adverse perinatal outcome.

Mechanisms by which ART may confer the risk of adverse perinatal outcomes remain unknown. It is likely that these may not be caused by ART per se, but rather associated with other factors such as the underlying infertility problem. It has been proposed, however, that the substantial endocrine changes caused by aggressive COS regimens, laboratory interventions and altered gene expression in the placenta may contribute to adverse perinatal events after ART treatment.[17,21]

Risks to offspring

A pooled estimate from 45 cohort studies found that infants born following ART treatment have a 32% increased risk of congenital anomalies compared to those conceived naturally (relative risk [RR] 1.32, 95% CI 1.24–1.42). The risk further increased to 36% (RR 1.36, 95% CI 1.30–1.43) for singleton births when examined separately and to 42% (RR 1.42, 95% CI 1.29–1.56) for major anomalies requiring surgical correction.[22] Again, the exact mechanisms underlying these findings are unknown, but it is possible that the increased risk is partly attributed to the underlying infertility in parents. A Danish registry study, which considered singletons born to fertile couples as a reference, found a higher incidence of congenital anomalies in singletons born of subfertile couples who conceived naturally (HR 1.20, 95% CI 1.07–1.35) and in treated infertile couples (HR 1.39, 95% CI 1.23–1.57).[23]

Although the data from these studies suggest a 30–40% increased risk of congenital malformations following ART treatment, when counselling people, it is important to inform them that the absolute risk remains low. For a background prevalence of 5%, an increase of congenital malformations of 30–40% results in an absolute risk of 6.5–7.0%.[24]

Epigenetics refers to genomic information over and above that contained in the DNA sequence.[22] Epigenetic regulation is crucial to genome function. Epigenetic alterations to imprinted genes can cause imprinting disorders, including childhood genetic disorders such as Prader–Willi, Angelman and Beckwith–Wiedemann syndromes, as well as several types of cancer including Wilms tumour. A systematic review of four studies (three cohort studies and one case–control study) found an association between ART and the risk of epigenetic and imprinting syndromes in children conceived following ART treatment. Furthermore, it suggested that children conceived following ART treatment had a higher risk of any imprinting disorder than spontaneously conceived children, with a combined odds ratio (OR) (95% CI) of 3.67 (1.39–9.74).[25]

The evidence that young men born from ICSI treatment have reduced semen parameters[26] favours the argument that ICSI should not be used routinely, but only where there is a defined male factor.

Childhood cancer risk

Childhood cancer is the second most common cause of death in children in developed countries. The exact cause of childhood cancer remains largely unknown. It has been hypothesised that some cancers are initiated during the early stages of fetal development and, therefore, any events leading up to and around the time of conception may be important. Many studies have evaluated the potential childhood cancer risk in children conceived following ART treatment. Although some have suggested a possible increased risk, it has not been possible to unravel the absolute effects of ART from other factors such as the underlying infertility problem and familial predisposition.

Data from the Swedish Cancer Registry showed an increased risk of childhood cancer for children born following ART treatment compared to spontaneously conceived children (RR 1.42, 95% CI 1.09–1.87).[27] However, a large British cohort study[28] found no significant increase in the overall risk of childhood cancer (standardised incidence ratio [SIR] 0.98, 95% CI 0.81–1.19) or most childhood cancer subtypes. In a meta-analysis of observational studies, an association between fertility treatment and childhood cancers was found, but the risk estimates for overall cancer and haematological cancer following ART treatment were not significant.[29] A retrospective Nordic population-based cohort study published in 2014 suggested no significant increase in overall cancer rates in children (adjusted HR 1.08, 95% CI 0.91–1.27) born as a result of ART treatment compared to spontaneously conceived and born children.[30] The largest population-based study found no association between the maternal use of fertility drugs and the overall risk of childhood cancers, except that exposure to maternal progesterone markedly increased the risk of acute lymphocytic leukaemia and sympathetic nervous system tumours.[31]

Factors affecting reproductive outcome of assistant reproductive technology treatment

One of the commonest questions asked in the clinic by those considering ART treatment is: 'what are the chances of our treatment being successful?' Various factors determine the success of an ART cycle (Table 2) and it has been suggested that up to 50% of people choosing ART remain childless despite undergoing multiple treatment cycles.[32] Accurately predicting the potential effectiveness of ART treatment will be invaluable to practitioners to offer individualised counselling. Since there is no group with a 100% success rate, using cumulative pregnancy rates would be more useful than success per cycle.

Female age

Female age is the strongest predictor of ART success, with the odds of achieving pregnancy following ART treatment

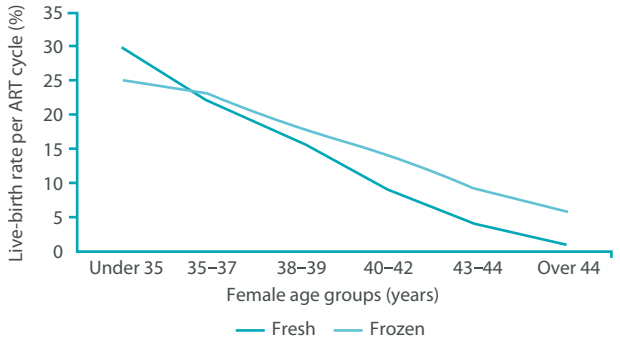

Figure 2. Female age and assisted reproductive technology (ART) success. Human Fertilisation and Embryology Authority data from 2015 suggests an age-related decline in birth rate following ART.[6]

becoming lower with increasing female age.[33] HFEA data from 2015 based on 72 504 cycles of ART treatment clearly demonstrate a decline in LBR per ART cycle with an advancing maternal age (Figure 2).[6] A study of 5 years of HFEA data examined the predictors of live birth following ART treatment and suggested that the probability of a successful live birth decreases with maternal age over 35 years.[34] Age-related decline in female fertility and ART success is mostly attributable to decreased ovarian reserve and oocyte quality along with a higher aneuploidy rate. Decreased ovarian reserve commonly leads to poor ovarian response to COS. Poor quality oocytes and an increased aneuploidy rate in oocytes leads to failed/abnormal fertilisation, fewer embryos available for transfer and higher miscarriage rates.

For older women, the use of donor oocytes is a successful strategy to increase the chances of a live birth. HFEA data from 2015,[6] shown in Figure 3, suggests that the LBR per ART cycle using donor oocytes is similar irrespective of the recipient age group.

Previous obstetric history

Previous pregnancy and live birth significantly increases the odds of a successful live birth with future ART treatment.[34] Previous spontaneous pregnancy and live birth increases the odds of a successful pregnancy by 19%, whereas live birth as a result of ART treatment increases the chances of a future live birth with ART treatment by 58%.[34] These findings suggest that ART plays a key role in solving a definite fertility problem. On the contrary, an inverse relationship also exists between the number of previous failed attempts and successful live births. The chance of a live birth decreases rapidly after four prior unsuccessful ART treatment attempts (OR 0.55, 95% CI 0.45–0.69)[34] and a longer duration of infertility results in a decrease in continuing pregnancy rate (OR 0.99, 95% CI 0.98–1.00).[33] The LBR appears to be particularly affected when there have been more than 7 years of infertility.[34]

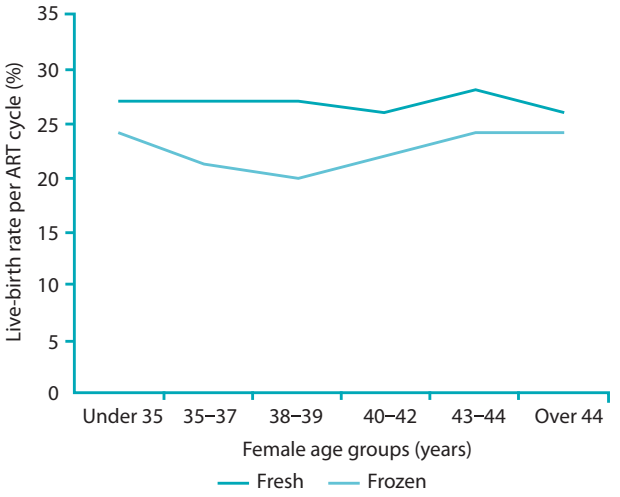

Figure 3. Assisted reproductive technology using donor eggs. Human Fertilisation and Embryology Authority data from 2015 suggests that the birth rate using donor oocytes is similar irrespective of the recipient age group.[6]

Maternal body mass index

Although there are other reasons to optimise the female partner's weight before contemplating pregnancy, there is a lack of consistent good quality evidence to suggest the effects of body mass index (BMI) on the success of ART treatment. Two earlier systematic reviews of observational studies, published in 2007[35] and 2011,[36] demonstrated a possible harmful effect of obesity on pregnancy outcome. However, a more recent systematic review from 2012[37] found no significant decrease in pregnancy and LBR following ART treatment in overweight and obese women compared to women of normal weight. Obese women carry significant risks to themselves and the unborn fetus, with increased rates of congenital anomalies, miscarriage, fetal growth disorders (macrosomia and growth restriction), stillbirth, gestational diabetes, hypertension, venous thromboembolism and problems during birth including increased caesarean section rate and postpartum haemorrhage. Hence, obese women are advised to achieve a BMI of (preferably) less than 30 before starting any form of fertility treatment.[38]

Lifestyle

Anecdotally, clinicians more frequently see couple who wish to know which lifestyle behaviours they should modify to maximise the probability of conception and successful ART treatment. However, research on the effects of lifestyle habits of people undergoing ART treatment and reproductive outcome is limited, and the few studies that have been published are mostly retrospective in nature. Observational studies suggest that excess alcohol consumption,[39,40] smoking[41] and caffeine consumption[42,43] may negatively

influence ART outcome. NICE guidelines suggest that more than 1 unit of alcohol per day, maternal and paternal smoking and maternal caffeine consumption reduces the effectiveness of ART.[15]

It has been speculated that various types of alcohol may have different biological influences on reproduction, but the exact effects are mostly unknown. A multicentre prospective study associated female alcohol consumption with a decrease in the number of oocytes retrieved, increased risk of failing to achieve pregnancy and a higher risk of miscarriage.[39] Another prospective study demonstrated a reduction in LBR with IVF with the consumption of as few as four alcoholic drinks per week.[40]

The exact mechanism by which smoking negatively affects the outcome of ART treatment is poorly understood. Pooled data from four studies included in a meta-analysis, which reported on 3252 ART cycles for smokers and 4213 cycles for non-smoking controls, demonstrated a significantly decreased LBR per cycle for smokers (OR 0.54, 95% CI 0.30–0.99).[41]

Caffeine has been shown to reach follicular fluid, with a negative effect on the number of oocytes retrieved and increased miscarriage rates.[43] A prospective study on female consumption of caffeine found caffeine to be a strong risk factor for reduced live birth following ART treatment.[42]

While good quality evidence on the association between lifestyle factors and ART outcomes is limited, treating clinicians are recommended to encourage women to modify these habits before commencing ART treatment and to guide them to appropriate lifestyle modification education programmes that may lead to a better ART treatment outcome. It is well established that lifestyle behaviour change can significantly affect quality of life and lifespan.

Number of oocytes retrieved

In a systematic review and meta-analysis,[33] the authors found a significant positive association between the number of oocytes retrieved and the odds of pregnancy (summary OR 1.04, 95% CI 1.02–1.07). Analysing HFEA data from 400 135 ART cycles, Sunkara et al.[44] suggested that the number of oocytes retrieved in the course of ART treatment is a robust surrogate marker for a positive clinical outcome, with LBR rising with increasing number of oocytes up to around 15, after which it plateaus and declines beyond 20 oocytes. Poor ovarian response associated with increasing maternal age may be responsible for the retrieval of fewer oocytes and a reduced chance of pregnancy. On the other hand, lower LBR with a higher number of eggs could be caused by suboptimal oocyte quality or an associated endocrinological imbalance affecting embryo implantation.[44]

Ovarian reserve markers

In current clinical practice, serum anti-müllerian hormone (AMH), produced by the granulosa cells of the pre-antral follicles, and antral follicle count (AFC), the number of follicles visible on a transvaginal ultrasound scan, have been acknowledged as the best available ovarian reserve markers. AMH reporting has now become standardised. The objectivity of serum AMH testing means it is a better-accepted biomarker for evaluating ovarian reserve and for predicting ovarian response, whether poor or excessive, to stimulation.[45] A cut-off AMH value of between 0.7 and 1.3 ng/ml and 3.36 ng/ml (Diagnostic Systems Lab assay) is commonly used to predict poor ovarian response and hyper response to COS, respectively.[46] AFC is strongly related to serum AMH levels and is equally capable of ascertaining over-response[47] and under-response.[48] A cutoff AFC of between <5–7 and >16 provides an accurate prediction of diminished and hyper response, respectively.[46] However, if a good quality embryo is replaced, AMH and AFC do not predict treatment success.

Male factors

Male factors are responsible for approximately half of fertility problems in male–female couples. Routine semen analysis provides information about sperm production and delivery, but limited information about sperm function. Although there is a direct relationship between semen quality and ART treatment outcome, there is no definite predictive threshold for success for conventional semen parameters.[49] Functional assessment of sperm by evaluating sperm DNA fragmentation has been proposed, but a systematic review published in 2016 concluded that current sperm DNA fragmentation tests have limited capacity to discriminate between good and poor ART treatment prognosis.[49] Sperm anti-sperm antibodies are believed to have an adverse impact on male fertility. However, there is a lack of good evidence to suggest a relationship between anti-sperm antibodies and pregnancy rates following ART treatment.[50]

Fertilisation method

ICSI is a procedure in which a single sperm is injected directly into an oocyte. It is recommended for severe male factor infertility, ART treatment with surgically retrieved sperm and for previous poor fertilisation[15] to increase the chance of fertilisation and a live birth. ICSI may also be used for certain ART procedures such as pre-implantation genetic diagnosis or screening to allay the risk of non-fertilising sperm cells contaminating the genetic analysis. There is no significant advantage of routinely using ICSI over IVF for all people choosing to use ART, or for those undergoing ART treatment for non-male factor infertility, but ICSI requires unnecessary additional resources, effort, time and laboratory experience.[51]

Embryo quality

Embryos are generally assessed at specific time intervals throughout the incubation period. Morphological evaluation for blastomere number, size and fragmentation using light microscopy remains the first-line approach in determining

cleavage stage embryo quality (Figure 4a and 4b).[52] Blastocyst grading is based on the rate of blastocoele expansion and characteristics of the inner cell mass and trophectoderm (Figure 4c and 4d).[52]

Better embryo quality is associated with higher chances of pregnancy[53] and ET at the blastocyst stage significantly improves LBR (OR 1.40, 95% CI 1.12–1.74) compared to ET at the cleavage stage.[54]

Number of embryos transferred

Pooled data from a Cochrane review[55] suggests that women who had single embryo transfer (SET) are likely to have a significantly lower LBR in a fresh cycle than those who had double embryo transfer (DET) (OR 0.48, 95% CI 0.39–0.60). However, the cumulative LBR between a single cycle of DET was not found to be significantly different to repeated SET – either SET followed by transfer of a single frozen embryo in a natural or hormone-stimulated cycle (OR 0.83, 95% CI 0.61–1.12) or two fresh cycles of SET (OR 0.79, 95% CI 0.36–1.72). Moreover, multiple pregnancy rates following SET were significantly lower compared to DET (OR 0.03, 95% CI 0.01–0.13).

Interventions to improve treatment success

Many proposed interventions (add-ons) are offered by assisted conception clinics in an attempt to improve the success of ART treatment. Some of these emerging techniques show promising results in initial studies; the others are empirical. Table 4 summarises some of the

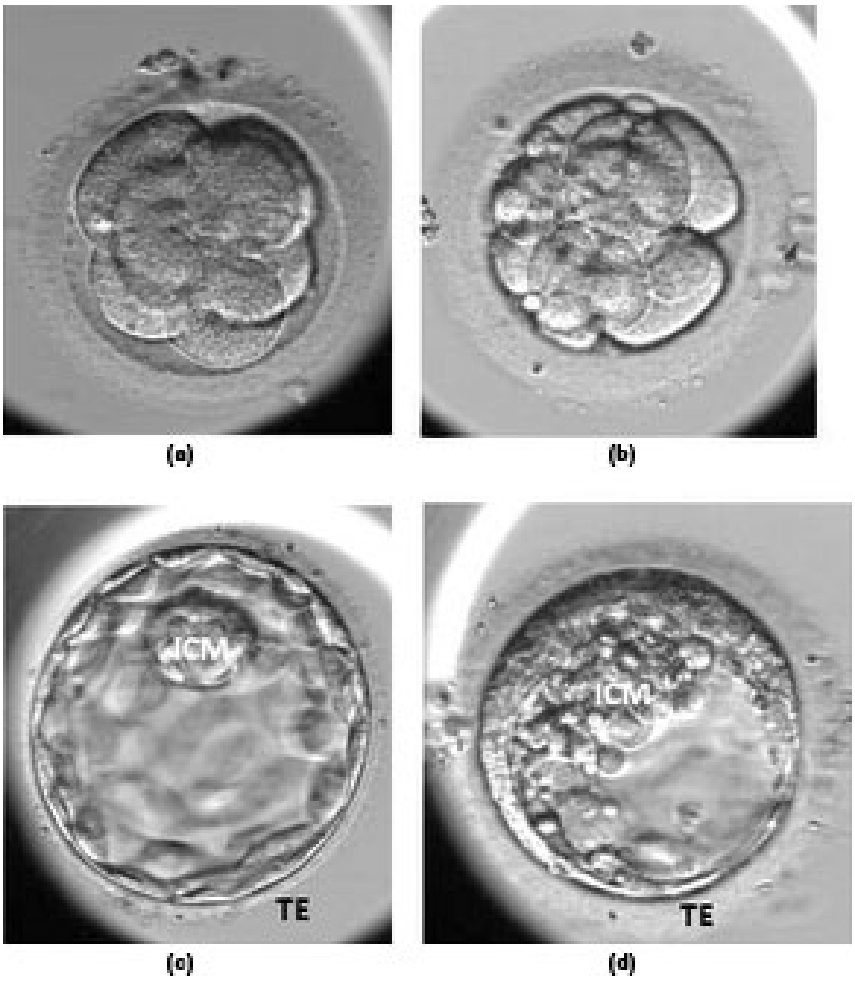

Figure 4. Good- and poor-quality embryos: a) good-quality cleavage-stage (day 3) embryo with eight cells which have stage-specific size/evenness for most blastomeres and 10–20% fragmentation; b) poor-quality cleavage stage (day 3) embryo with seven cells, majority of blastomeres with different sizes/evenness and around 50% fragmentation; c) good-quality blastocyst (day 5), which is nicely expanded and has a prominent inner cell mass (ICM) in which the cells are tightly compacted and a continuous layer of small identical cells in the trophectoderm (TE); d) poor-quality blastocyst (day 5), although expanded well, very few cells of inner cell mass are visible and there are fewer small cells in the trophectoderm (TE) which are not continuous. Images not to scale.

Table 4. Human Fertilisation and Embryology Authority ratings for interventions (add-ons) commonly employed in UK practice to improve the success of assisted reproductive technology (ART) treatment[56]

Intervention	Percentage of clinics use in UK (%)	Evidence
Interventions for which there is a growing body of promising evidence, but further research is still required:		
Endometrial scratch	60	No evidence of benefit before first ART cycle. May benefit women with two or more previous ART failures.
Time-lapse imaging	56	Insufficient evidence to suggest improved live birth rates.
Day 5 pre-implantation genetic screening (PGS)	32	Might be beneficial in selected groups: younger women typically under the age of 37 years with no history of miscarriage or failed in vitro fertilisation cycles.
Hyaluronic acid	25	Moderate quality evidence suggests improved pregnancy and live birth rates.
Elective freezing of all embryos	10	Insufficient evidence to confidently recommend this intervention.
Egg activation with calcium ionophore	1	Early results are promising but more evidence is needed.
Interventions for which there is no available evidence to show that the add-on is effective and safe:		
Assisted hatching	59	Not been shown to improve pregnancy rates.
Day 3 pre-implantation genetic screening (PGS)	32	No evidence to show that PGS carried out on day 3 embryos is of benefit. Can reduce success rates, probably because of damage to the embryo.
Reproductive immunology	18	No benefit. Risks attached to these treatments, some very serious.
Intra-uterine culture	1	No evidence to suggest improved outcome or safety.

common add-ons currently offered in UK clinics and the available evidence on their safety and effectiveness.[56]

Conclusion

ART is associated with several short-term and long-term complications that affect both the potential mother and her child or children. Healthcare professionals providing ART treatment must be fully aware of these complications, appreciate certain limitations of the available evidence and use the information to support people before, during and well after their course of treatment. Clinicians should also be aware of the factors determining ART success and the available evidence regarding the efficacy and safety profiles of ART add-ons. This would enable clinicians to have honest discussions with those seeking ART treatment before recommending the appropriate treatment and interventions.

Disclosure of interests

There are no conflicts of interest.

Contribution to authorship

All authors contributed to the conception and design of the study. HMB conducted the literature search, and drafted the article. MKC and JAS critically revised the manuscript for important intellectual content.

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