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Assisted reproductive technology: Short- and long-term outcomes

Mary Elaine Graham[1], **Angie Jelin**[2,3], **Alexander H. Hoon Jr**[4,5], **Anna Maria Wilms Floet**[4,6,7], **Eric Levey**[8], **Ernest M. Graham**[3,9]

[1]College of Arts and Sciences, Washington and Lee University, Lexington, VA, USA

[2]Department of Genetic Medicine, Johns Hopkins University School of Medicine, Baltimore, MD, USA

[3]Department of Gynecology and Obstetrics, Division of Maternal-Fetal Medicine, Johns Hopkins University School of Medicine, Baltimore, MD, USA

[4]Department of Pediatrics, Division of Developmental Medicine, Johns Hopkins School of Medicine, Baltimore, MD, USA

[5]Phelps Center for Cerebral Palsy and Neurodevelopmental Medicine, Kennedy Krieger Institute, Baltimore, MD, USA

[6]Center for Autism and Related Disorders, Kennedy Krieger Institute, Baltimore, MD, USA

[7]Center for Development and Learning, Kennedy Krieger Institute, Baltimore, MD, USA

[8]Health Services for Children with Special Needs, Washington, DC, USA

[9]Neuroscience Intensive Care Nursery Program, Johns Hopkins University School of Medicine, Baltimore, MD, USA

Abstract

Assisted reproductive technology (ART) includes fertility treatment in which either eggs or embryos are handled outside a female's body to promote successful pregnancies and healthy offspring. Current ART procedures encompass in vitro fertilization with or without intracytoplasmic sperm injection. The most common complication of ART is related to the consequences of multiple pregnancy, which can be prevented or minimized by reducing the number of embryos transferred to the uterus, commonly single embryo transfer. ART has been shown to be variably associated with adverse short- and long-term perinatal outcomes, including cerebral palsy, autism, neurodevelopmental imprinting disorders, and cancer. However, there is uncertainty as to whether reported problems are related to the ART procedure itself, to factors related to infertility, to other medical and environmental factors, or a combination thereof. From a pathophysiological perspective, whether ART alters epigenetic mechanisms of gene expression, leading to later developmental, medical, and behavioral disorders, is an area of active

Correspondence: Alexander H. Hoon Jr, Kennedy Krieger Institute, 801 North Broadway, Baltimore, MD 21205, USA. hoon@kennedykrieger.org.

investigation. With the meticulously conducted short- and long-term outcome studies completed so far, overall, and after controlling for multiple gestations and preterm delivery, the results suggest that ART is a safe procedure, offering hope to many parent(s) wishing for a healthy child. This paper highlights ART methods and the risk factors and confounders in the interpretation of short- and long-term outcome data, providing the reader with a means to evaluate findings and conclusions of outcome studies.

In 1978 Louise Joy Brown was the first infant born by in vitro fertilization (IVF), as the result of the pioneering work of Robert Edwards, Patrick Steptoe, and Jean Purdy in the successful development of this procedure.[1,2] This dramatic success was followed 14 years later by the first infant born after intracytoplasmic sperm injection (ICSI),[3] a method that was initially developed for male infertility.

These and subsequent advances in the rapidly developing field of assisted reproductive technology (ART) have provided hope for people struggling with the medical, emotional, and financial effects of infertility and for those wanting to conceive where there are risks of the recurrence of monogenic disorders.[4,5] As of 2020, an estimated 8 million children had been conceived by ART.[6]

ART refers to in vitro procedures with carefully orchestrated sequential steps, which are overall termed an ART cycle: ovarian stimulation; surgical removal of eggs from the ovary; fertilization with sperm in a laboratory; and then returning embryo(s) to the female reproductive tract. ART can involve donor eggs, donor sperm, and gestational carriers. Procedures include IVF and ICSI. There are situational indications for either fresh or frozen embryo transfer.[7,8]

Since inception, ART procedures have been rapidly modified and integrated into fertility management (Figure 1).[9–12] Overall these changes have made it challenging to evaluate short- and long-term outcomes with sufficient numbers to minimize confounders. This has also created challenges in providing preconception counseling about outcome risks.[13]

ART is associated with a wide range of complex ethical, moral, and financial questions including upper age limits for ART, the ‘ownership’ of gametes and embryos, intrafamilial gamete donation, IVF use in single females and same sex couples, the use of preimplantatory genetic testing, social egg freezing, commercialization, public funding, and prioritization of IVF.[14,15]

In this regard, providing informed consent for people desiring a child through ART is extremely challenging. There are important considerations from patient, provider, payer, and societal perspectives, involving both facts and values. In the setting of ART, facts change with technological advances and values evolve with societal changes—both affecting the consent process. Oral and written consent are important components of informed consent. Oral consent establishes open communication and shared decision making; written consent promotes educational understanding and serves as legal documentation.[16]

People considering ART bring individual hopes, fears, and wishes—with variable understanding of the ART procedure itself, complex emotional feelings linked to personal, familial, cultural, and religious expectations and beliefs, differing appreciation of risks, benefits, and potential outcomes, and often concerns about associated costs.

From the clinician's perspective, providing informed consent requires extensive knowledge as well as awareness of internal biases in determining who would be an appropriate candidate for ART.[17] Extensive knowledge of the underlying risks to conceive successfully, an understanding of specific goals and outcomes, and a recognition of the financial costs involved is essential. A further important factor to consider is that there are ongoing improvements in ART technology so no studies of short- and long-term outcome can be 'up to date'. Importantly, like patients and families, clinicians have their own belief systems as to what is appropriate in any given situation which must be recognized.[15]

The costs of ART are variably covered by public funding, private health insurance, out-of-pocket funds, or a combination thereof. For example, in the USA in 2016, the average cost of one IVF cycle was $10 000 to $15 000.[18] From a societal perspective, with financial, cultural, religious, and political sensibilities, there is great diversity in ART practice.[19]

With all these factors to consider, patients are in a position to make the best decisions for themselves when the provider presents information in a straightforward manner, so that patients can use their own common sense, personal instincts, and beliefs to make informed decisions on how to proceed.

ART has been variably associated with a range of adverse obstetric and perinatal outcomes, birth defects and neurodevelopmental disorders, as well as adult disorders including obesity, early onset diabetes, and cardiovascular disease.[20] With reports of short- and long-term consequences, the question remains whether these reported outcomes are secondary to the procedures themselves, to the postponement of childbearing, or to factors related to underlying maternal or paternal infertility. An important requirement is human studies with adequate sample sizes and appropriate comparison groups to fully assess these risks. Furthermore, specific differences in methodologies, such as the media used, are not standardized or reported in a uniform manner.

From the perspective of clinicians evaluating patients with developmental delay or neurodevelopmental disorders conceived by ART, knowledge of underlying risk factors and the procedures themselves, including an understanding of potential epigenetic mechanisms, is an important component of the diagnostic evaluation.

To address the complex relationship between ART and outcome from the prenatal/perinatal period and extending through adulthood, we have divided this paper into two parts. The first section will focus on specific medical and technical aspects of ART. Potential alterations in epigenetic and other mechanisms will be discussed, with the recognition that the importance of specific factors related to outcome has not been fully established. The second part will focus on clinical outcomes—from the perinatal period through adulthood, discussing challenges in evaluating outcome studies, with the focus on ART singletons, as ART multiples have additional potential risks, which are linked to preterm birth.

This review should be read with a recognition of the challenges required to fully integrate the rapid advances in ART technology, with expansions to individuals beyond heterosexual couples and the variability in short- and long-term outcome, and viewed as a guide to focus diagnostic questions in the clinic rather than to provide ‘answers’. For clinicians evaluating children conceived by ART, care is required not to imply that the ART is the underlying etiological cause of a medical or developmental disorder, unless this can be clearly established. The rapidly expanding literature should be investigated with the understanding that up-to-date expertise is required.

CONCEPTION

Infertility is defined as a disease of the male or female reproductive system defined by the failure to achieve a pregnancy after 12 months or more of regular unprotected sexual intercourse.[21] While global epidemiological data are variable in content and depth, infertility affects as many as 186 million people worldwide.[22] Male infertility is an underlying cause in approximately one-third of couples and female infertility in one-third, with one-third undetermined or involving both partners.[23] Male infertility has a variety of causes, including genetic mutations, medical illnesses, medications, and lifestyle factors. Female infertility is often related to reduced ovarian reserve, ovulatory dysfunction, and structural abnormalities. Stress, anxiety, and depression are postulated risk factors, but have not been definitively established.[24]

For some couples, fertility education is sufficient for conception. Recommendations include appropriate timing of intercourse or making lifestyle changes, such as cessation of smoking and drug use or dietary changes.[25] For others, hormones to promote ovulation, medical treatment of disorders including diabetes, or surgical procedures for tubal occlusion may lead to a successful pregnancy. ART can be considered when these approaches are unsuccessful.

When a patient undergoing ART has a concern about a possible genetic disorder, preimplantation genetic testing (PGT) is often used. There are now three types of PGT: PGT-aneuploidy, PGT-monogenic, and PGT-structural rearrangement. PGT-aneuploidy is helpful in cases where there is a risk of embryo aneuploidy, such as with advanced maternal age, recurrent pregnancy loss, repeated implantation failure, severe male infertility factor, or when a single embryo transfer is necessary,[26] with the recognition of possible false positive results from this testing.[27] PGT-monogenic is generally performed when a parent has an identified mutation for a single-gene disorder. Finally, PGT-structural rearrangement assists in identifying whether a parental structural rearrangement is unbalanced in the embryo.[28]

After conception, chorionic villus sampling and amniocentesis remain common forms of prenatal diagnosis. Uptake for prenatal diagnosis has significantly declined with the availability of multiple prenatal aneuploidy screening options, which have rapidly evolved to include first- and second-trimester serum analytes, nuchal translucency ultrasound, ‘genetic sonogram’, and cell-free DNA. There are also many parental carrier screening options for single-gene disorders.[29]

EMBRYONIC AND FETAL DEVELOPMENT

To understand ART procedures and their potential risks, background knowledge of embryonic and fetal development is necessary. The initial fusion of egg and sperm gametes results in a diploid zygote (Figure 2).[30] Cleavage divisions of the zygote occur every 12 to 24 hours, with individual cells at this stage termed a blastomere. At one day after the eight-cell stage the zygote becomes a morula, at which time all cells are totipotent. The morula subsequently develops into a blastocyst on day 5. Natural implantation occurs during days 8 to 9.

Advances in culture media have led to a shift in IVF from cleavage stage embryo transfer to blastocyst stage transfer, with the belief that blastocyst transfer will improve uterine and embryonic synchronicity and enable self-selection of viable embryos, leading to improved rates of live birth. PGT, when indicated, is now also performed at the blastocyst stage. However, it remains unclear whether the day of transfer has a beneficial effect on live birth and pregnancy rates.[31,32]

Embryonic development extends from fertilization through the 10th week of pregnancy, during which time organs and body structures are formed. Fetal development begins at the 11th week (the 9th week after fertilization) and continues until birth. Embryonic and fetal development are precisely temporally and spatially organized. This elegant process is guided both by genomic mechanisms and by the environment, including maternal nutrition.[33,34]

EPIGENETICS

Epigenetic refers to heritable and environmental changes in gene expression that are not due to changes in the DNA sequence. The molecular mechanisms underlying epigenetic expression are complex and incompletely understood, but broadly include DNA methylation at CpG nucleotides, imprinting, non-coding RNAs, covalent modifications of histone proteins, and remodeling by other chromatin-associated complexes. Epigenetic mechanisms are primarily mitotically heritable and underlie the patterning required for typical development and for gene expression in diverse cell types throughout life.[35,36]

Epigenetic reprogramming is an essential process for normal zygotic and embryonic growth and development. Reprogramming occurs during gametogenesis and early embryogenesis. As such, anything that disrupts this reprogramming can affect gene expression, leading to deleterious consequences later in life. In this regard, ART procedures alter the environment of both male and female gametes and embryos when epigenetic imprints are being established.[37,38] These include the methods of ovarian stimulation/ovulation, exposures of gametes and embryos to the in vitro environment in which they mature with changes in temperature, pH, and oxygen tension, and freeze–thaw embryo manipulations.[39]

Many other factors may also play a role in epigenetic expression including underlying etiologies of infertility. Studies report varying degrees of certainty that either or both genetic and environmental factors, including the media used and manipulation of the gamete, zygote, or embryo, have effects on epigenetic expression, while the long-term consequences of such changes are not known.[38,40]

ENVIRONMENTAL FACTORS

Although the data are inconclusive overall, a wide range of environmental factors have been associated with infertility.[41,42] These include obesity, tobacco use, alcohol consumption, recreational drugs, nutrition, and environmental contaminants. There is evidence that lifestyle factors can affect the epigenetic blueprint of spermatozoa, with subsequent effects on embryonic development and offspring phenotype later in life.[43]

Another important environmental factor affecting fertility and outcome is stress.[25] Stress is complex, with effects on sexual function, fertility, and fetal outcome, mediated through the hypothalamic–pituitary–adrenal axis.[44] Both acute and chronic stress have been associated with disorders in pregnancy, neonatal morbidities, and subsequent neurodevelopmental disorders. In terms of non-pharmacological approaches, a wide range of interventions mitigating the effects of stress include meditation techniques, yoga, exercise, and expressive writing.[45] The relation between maternal stress, epigenetic imprinting, and outcome is being actively investiged.[46]

ART SELECTION

Evaluation for infertility is generally not recommended until a couple has attempted 12 months of frequent, unprotected intercourse without conceiving, unless the female partner is greater than 35 years of age, in which case evaluation after 6 months is recommended.[47] A medical history and physical examination are initially performed for both the male and the female partner.[48]

The evaluation of male fertility includes sexual history and a semen analysis. Personal history may include symptoms suggestive of erectile or ejaculatory dysfunction. Semen analysis is initially evaluated for quantity, morphology, and motility of sperm. If abnormal, additional testing is done to identify causes which may include structural and functional sperm abnormalities. Treatment options vary depending on the cause, including surgical correction of structural abnormalities.[49] Sperm retrieval techniques can also be performed.[50]

For male infertility, ICSI is often the first choice.[51] While ICSI has also been used for non-male factor infertility, there is ongoing debate about its use in this clinical situation.[52,53] Although earlier reports described a higher prevalence of de novo chromosomal abnormalities, a recent systematic review and meta-analysis with only weak evidence did not support this finding.[54]

The evaluation of female infertility is more complex. Because the most common cause of female infertility is ovulatory dysfunction, ovulation is initially confirmed.[47] If ovulation is confirmed, the next step is to evaluate for structural anomalies of the uterine and tubal anatomy using ultrasound and/or a hysterosalpingogram. The evaluation for anovulation includes hormonal evaluation. More invasive testing is available for females with specific symptoms.[47] Even after this comprehensive work-up, at times an underlying cause for either male or female infertility is not identified.

Depending on the cause identified, ART may be the treatment of choice. ART for female infertility typically involves IVF. Before trying IVF, intrauterine insemination can be attempted for females under 40 years of age.[48] Treatment selection also depends on factors such as success of treatments, age of patient, cost, and risk of genetic disease. Currently IVF is done in approximately one-third of ART cycles and ISCI in two-thirds. Couples who have unsuccessful outcomes with IVF can consider oocyte donation. If a parent is at high risk of transmitting a genetic disorder, PGT, donor insemination, and/or oocyte donation can be considered.[55]

PROCEDURES

In IVF, eggs are extracted after ovarian stimulation. Ovarian stimulation is used to facilitate retrieval of multiple oocytes during a single IVF cycle. A sperm sample is also obtained. After stimulation of the ovaries and retrieval of the eggs, the eggs are then fertilized in a Petri dish to create embryos. One or more embryos can be transferred in most females, and the spare embryos can be frozen for future pregnancy, avoiding the need for repeated ovarian stimulation and oocyte retrieval.[56] There are several methods for sperm selection.[57]

In ICSI, a single spermatozoon is injected into the oocyte cytoplasm. The mature oocyte is held with a specialized pipette. A very delicate, sharp, and hollow needle is used to immobilize and pick up a single spermatozoon. The needle is then carefully inserted through the shell of the oocyte and into its cytoplasm. The spermatozoon is injected into the cytoplasm, and the needle is removed. The oocytes are checked the following day for evidence of normal fertilization. Once fertilized, embryos can be transferred immediately back into the uterus (fresh transfer) or frozen for later implantation. If a patient would like another infant or if previous cycles were unsuccessful, and if the patient has remaining embryos from a previous cycle, the frozen embryos can be used. ICSI is more commonly recommended when there is male infertility relating to problems with sperm number or function.[58] There is ongoing controversy about whether ICSI should be used for non-male infertility.[59]

Patients who desire to have genetic testing of their embryo will freeze the embryo while awaiting the results of the testing. In general, the selection of fresh or frozen embryos should be considered on an individual basis.[8] With fresh embryo transfer, the embryo is transferred 3 to 5 days after the retrieval. In this situation, estrogen from the ovarian follicles helps prepare the endometrium for implantation. With a frozen embryo transfer, the embryo can be transferred months or years later. In this situation, estrogen patches, pills, or shots may be used to prepare the uterine endometrium.

There has been much controversy about the most appropriate embryo culture medium. Although an optimal medium is important for embryonic development and subsequent success of IVF or ICSI, there is insufficient evidence to support or refute the use of any specific culture medium.[60]

ANIMAL STUDIES

With the rapid advances in ART technology and methodology, preclinical studies in animals have been essential to evaluate ART safety and efficacy in humans.[61] These studies give us the opportunity to analyze the effects of each step of ART procedures.[62] Animal studies have involved gametes, preimplantation embryos, fetuses, and offspring in several generations —evaluating epigenetic, developmental, and transgenerational effects. Basic research has been essential in developing IVF methods, embryo culture, cryoprecipitation methods, and metabolic assays of embryo health.[63] For example, mouse embryo assays play a critical role in IVF media quality control and in cryopreservation protocols.[64] Studies also involve the use of murine, porcine, and bovine cell lines.[65] An important caveat in animal research is that there are species differences in genetic backgrounds, so that conclusions cannot necessarily be extrapolated to humans. Furthermore, there is a movement to reduce or replace animals in research.[61]

Animal studies have provided insight into the effects of ART on early fetal development. In terms of embryo culture, an increasing number of studies confirm the effect of culture media on early development, with inadequate media causing low implantation rates, disturbances in development speed, poor embryo quality, low trophoblast development, abnormal preimplantation epigenetic reprogramming, unbalanced fetal–placental development, and abnormal fetal growth. Embryo manipulation, including preimplantation genetic diagnosis and embryo transfer, has been shown to cause delays in development from one embryo stage to another.[66] In cattle, in vitro embryo production has been associated with lower pregnancy rates, early embryonic loss, prolonged gestation, and fetal overgrowth. In terms of later development, lifespan does not seem to be reduced if the animals are fed an optimal, balanced diet.[62]

In general, we can conclude from animal studies that ART procedures introduce metabolic disturbances affecting lipid and glucose metabolism. For example, changes to metabolism, gene expression, and placental size have been induced by IVF, ICSI, and superovulation. Overall, the placenta is important in the long-term effects of ART procedures, with abnormal placentation leading to long-term effects on metabolism and cardiovascular health.[62] Furthermore, mice born after blastomere biopsy had a deregulation of steroid metabolism, which can have severe effects on later development.[66] Culture media also have an effect, causing metabolic disturbances such as glucose tolerance and insulin resistance.[62] In addition, culture media were shown to be associated with higher systolic blood pressure in 21-week-old mice than in vivo controls. This study also found elevated activity of serum angiotensin and hepatic enzymes involved in the control of gluconeogenesis.[66] With regard to later metabolic disorders, mice conceived from ART were shown to be insulin resistant, despite having similar bodyweight. Altered liver phospholipid profiles linked to atherosclerosis and diabetes were observed in adult ART-conceived mice. Studies have also shown an increase in blood pressure in the adult mouse.[62]

Adding to this, animal studies shed light on behavioral effects of ART. For example, in young adult mice, the culture media used affects anxiety levels, memorization of spatial information, locomotor activity, and long-term memory.[62] Similar patterns were found in

ICSI-produced female mice compared with controls. Here, ICSI-produced females showed increased anxiety, lack of habituation pattern, deficits in short-term spatial memory, and age-dependent hypolocomotion in a variety of tests.[67] Furthermore, blastomere biopsy in mice caused antidepressant-like effects and deficits in habituation. Embryos biopsied at the four-cell stage had behavioral defects associated with increased hypomyelination of nerve fibers, neuronal degeneration, and abnormal expression of proteins involved in neurodegenerative disease, together with reduced methylation of the promoters of genes associated with neural disorders.[62]

In search of the mechanisms underlying some of these changes, researchers have investigated epigenetic alterations in animal models. Studies have found that superovulation, in vitro egg culture, and embryo manipulation produce epigenetic alterations in the egg and embryo, which can affect the outcome of the pregnancy and cause long-lasting effects.[66] For example, a signaling protein that protects cells from oxidative stress was upregulated in IVF blastocysts and in offspring adult muscle and fat. These observations were associated with increased histone H4 acetylation at the promoter in these tissues, thus demonstrating a direct link between epigenetic modifications in the embryo and in adult tissues.[62] The fertilization technique used also affects epigenetic alterations, with ICSI showing more epigenetic alterations than regular IVF. In particular, ICSI affected gene transcription and methylation of some epigenetically regulated genes such as imprinting, X-linked genes, and retro-transposon genes.[67]

Because the oldest cohort of ART-conceived humans are in their 30s and 40s, limited research has been done into the transgenerational effects of ART. Thus, we can look to animal studies to investigate possible outcomes. Multiple studies have shown that the epigenetic imprinting caused by ART can be transgenerationally transmitted. Specifically, studies with mice produced in vitro have found transgenerational transmission of cardiovascular phenotype and gene methylation patterns to the second-generation offspring through the paternal line.[62] Other studies have found transgenerational transmission of gene methylation patterns affecting the brain. IVF can also alter female reproduction in the next generation, as seen in a recent mouse study where suboptimal media culture was associated with transgenerational alterations of glucose metabolism and hepatomegaly in the male offspring.[66]

The true impact of ART into adulthood and across generations will not become apparent until more time passes and more research is done. For now, we can use animal studies to provide us with clues about possible outcomes.

ART AND OUTCOME OVERVIEW

Overall, there are significant differences in ART availability, use, and practice worldwide.[68] With this recognition, international registries reporting ongoing data about short- and long-term outcomes have been established to monitor trends and outcomes.[69,70] This temporal monitoring is important, as there are often changes in outcome over time, reflective of changes in both infertility risk factors and the procedures used.

One of the clearest risks to ART in general is the transfer of multiple embryos, tied closely to the increased risk for multiple birth and preterm delivery compared with singletons, and the concomitant impairments associated with preterm birth.[71,72] While there is variability on a world-wide basis, the general direction is towards single embryo transfer. This has been associated with a decreased risk for later neurodevelopmental disorders including cerebral palsy.[73]

An overriding etiological question remains one of 'chicken and/or egg'.[7] Specifically, do factors related to infertility lead to outcome, do ART procedures themselves contribute or, as is most likely, is it a combination of both, potentially compounded by other genetic and acquired factors? Additional elements that must be considered are changes in laboratory conditions including the variability in media used (Figure 3).[74]

An essential research component to address outcome risk is the nature of the comparison groups used.[75] While comparison groups are often selected from spontaneously conceived pregnancies, they do not have infertility as a common potential underlying factor. A more appropriate group would be spontaneous pregnancies in infertile couples, which is more difficult to establish. However, even in this situation an important confounding factor can be the difference in maternal age at the time of conception.

From a mechanistic perspective, while the mechanisms are probably multifactorial, epigenetic regulation of both imprinted and non-imprinted genes may play an important role in placental, gamete, and embryo epigenomes, leading to birth defects and chromosomal disorders, neurodevelopmental disabilities in childhood, as well as cardiometabolic disorders in adulthood,[7] consistent with the developmental origins of health and disease model.[76]

Outcome can be considered along two dimensions: (1) time—maternal/fetal/neonatal, childhood, and adult; and (2) medical—birth defects/malformation, developmental disability, psychiatric, and general medical.

MATERNAL AND PERINATAL OUTCOME

With regard to maternal/neonatal outcomes, there are health implications for both the mother and fetus/newborn with ART. From the maternal perspective, ART carries an increased risk of hypertensive disorders of pregnancy, placental complications including abruption and third trimester hemorrhage, preterm delivery, and the requirement of Cesarean section.[77,78] For singleton pregnancies, there is an increase in preterm birth, low birthweight, small for gestational age, stillbirth, and perinatal mortality.[79] As noted previously, it is important to recognize that other factors may also contribute to this risk, including underlying infertility and other biological factors, ovarian induction with supraphysiological levels of estradiol, and the ART procedures.[20]

When evaluating the risk of non-chromosomal birth defects in singletons, ART seems to be associated with a slightly increased risk for specific disorders, including cardiac, neural tube, palatal, gastrointestinal, and genitourinary,[80] although there is conflicting evidence here.[77] Postulated mechanisms include underlying infertility, ovulation induction medications, as well as micromanipulation of the embryo outside the uterus. In multiple gestations there is

also an increased risk of birth defects, without a clear mechanism for this. However, given the differing definition of what constitutes a birth defect and changes in ART methods, precise conclusions are difficult to determine.

With the increased incidence of preterm birth and low birthweight in ART singletons, there has been concern about postnatal growth. Outcome data are reassuring about growth into early adulthood, supporting catch-up growth.[81] Continued follow-up into later life will be needed to confirm this.

CHILDHOOD OUTCOME

With regard to intellectual disability, conclusions are like-wise tentative given differences in study methodologies, population differences, and follow-up periods. Some studies suggest increased rates of intellectual disability,[82,83] while a recent meta-analysis reported similar cognitive outcomes.[84] Current evidence suggests that ICSI may be associated with an increased incidence of intellectual disability compared with IVF,[83] but again there is variability.

In the past, outcome studies about the development of cerebral palsy have shown an increased risk with ART.[85] In a recent study from Western Australia using high-quality registry data, a high proportion of multiple embryo transfers showed a twofold increase in the prevalence of cerebral palsy. While these and other outcome studies have shown an increased risk for the development of cerebral palsy, multiple births and the increased risk of preterm birth are confounding factors.[86] A recent meta-analysis reported a greater than twofold increase in cerebral palsy, but the risk is largely due to increased rates of multiple births and preterm birth.[87] In support of this, there has been a substantial decrease in cerebral palsy in Nordic countries over the period 1990 to 2014 in parallel with increased single embryo transfer and decreased multiple births, in support of the ongoing trend to single embryo transfer.[73]

While the incidence of autism spectrum disorder and the use of ART have increased in parallel, whether there is an association remains unclear. As with potential risks associated with other outcomes, risk factors associated with infertility include older paternal age, sperm quality, and maternal infertility.[88] In a large longitudinal cohort study from a database linked to early-intervention participation data, there was no increase in autism spectrum disorder in IVF, ICSI, or in subfertile females.[89] Conversely, in a cohort study from a national registry, progesterone exposure during a specific time in fetal development increased the risk of autism spectrum disorder, with a postulated causal effect secondary to epigenetic modifications.[90] In a recent meta-analysis there was an increased overall risk of autism spectrum disorder, but this risk was not seen in singletons, again highlighting the additional risks associated with multiple births.[91] While some groups have provided data suggesting that the risk of autism spectrum disorder is greater with ICSI than with IVF, conclusive evidence has not been established.[92]

Although only a small number of children conceived by ART have been identified with imprinting disorders, there are studies reporting increased risks of congenital imprinting

disorders, including Beckwith–Wiedemann, Angelman, Prader–Willi, and Silver–Russell syndromes.[93,94] In a recent large register-based cohort study, the risk of an imprinting disorder was very small in general, with a possible increased risk of Beckwith–Wiedemann syndrome.[95]

With regard to the risk for childhood cancer, the data are, overall, cautiously reassuring. In a recent meta-analysis comparing ART with both naturally conceived children from subfertile females and children from the general population, no increased risk of childhood cancer was identified.[96] In a recent large register-based cohort study, IVF with or without ICSI was not associated with an increased risk of childhood cancer. There was, however, an increased risk of cancer, mainly childhood leukemia, when using frozen embryo transfer.[97] In a retrospective, population-based cohort study comprising 66% of US births and 75% of IVF-conceived births, there was a significantly increased risk of hepatic tumors, while the rates of other cancers did not differ.[98] As is the case with most outcome studies, the possibility of unknown confounders is broadly recognized as well as the need for longer-term outcome studies.

OUTCOME IN ADULTHOOD

With the increased awareness of the developmental origins of health and disease (Barker hypothesis),[99] there are concerns about the long-term risks of cardiometabolic disorders. As ART procedures were not successfully implemented until 1978, there are few data available beyond adolescence and early adulthood.

With regard to long-term cardiovascular health, human and animal model studies have shown that premature vascular aging is present in adolescents and young adults who were conceived with ART. With age, these findings progress to arterial hypertension. From a mechanistic perspective, it is speculated that epigenetic modifications may be involved.[100] With other studies minimizing this risk,[101] further research will be required to follow cohorts into later adult life. This seems to be limited to cardiovascular disease, with uncertainty about metabolic disorders including diabetes.[101,102]

When considering adult outcomes, it should be recognized that, given the time interval in years, a multiplicity of postnatal factors, both genetic and environmental, may play an important role in etiological antecedents. Given that children conceived by ART are just beginning to enter middle age, the long-term impact of ART will only become clear in the future.

CONCLUSIONS

In general, ART has the potential to have a life-changing impact for people who are otherwise unable to conceive; however, parents should be counseled on the risks and benefits.[103,104] In concordance with advanced medical technology, the benefits of ART are also associated with risks. Although the primary risks are more strongly associated with multiple births, even in singleton pregnancies there is an increase for specific birth defects, imprinting disorders, preterm birth, low birthweight, small for gestational age, stillbirth, and perinatal mortality. Neurodevelopmental outcomes are overall reassuring, with

risks disappearing when adjustments are made for multiple births. Furthermore, when risks persist, it is often for specific subgroups such as IVF compared with ICSI or with fresh embryo transfer compared with cryopreservation.[103]

The most well-established risk for a neurodevelopmental disorder is the implantation of more than one embryo, with the mechanism linked to an increased risk of brain injury in association with preterm birth. While Nordic countries, the UK, the Netherlands, Belgium, and even the USA have reduced multiple births after ART, many other countries have not adopted embryo implantation restrictions in this regard.[105]

Because the first IVF procedure was done in 1978, the oldest ART-conceived people are in their late 30s and early 40s. Given this, study of the long-lasting effects of ART in humans is not possible. There are limited studies on the effect of ART in young adults.

From the perspective of those involved, there are often complex emotional feelings about infertility. When considering ART, the uncertainty of the outcome should be addressed as sensitively as possible. Recognizing the complex medical, personal, ethical, legal, and financial implications of ART, we hope that this review will generate further interest and questions, rather than providing definitive answers, which are not currently available.

Planning for a baby is a cherished dream for the expectant parent(s). The background risks for a problem in any pregnancy are widely known and accepted, with the hope that everything will turn out right. Infertility and pregnancy bring increased risks of uncertain magnitude. While there are reasons for concern about IVF, it is incumbent on researchers and clinicians to conduct long-term studies with large populations and appropriate comparison groups, and to carefully and thoroughly document and characterize a wide range of outcomes.[106]

In summary, given the meticulously conducted short- and long-term outcome studies completed to date, results suggest that ART is a relatively safe procedure which offers hope to many parents wishing for a healthy child.

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Abbreviations:

ART	assisted reproductive technology
ICSI	intracytoplasmic sperm injection
IVF	in vitro fertilization
PGT	preimplantation genetic testing

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What this paper adds

- Assisted reproductive technology (ART) is a relatively safe procedure.
- Single embryo implantation optimizes outcome.
- Informed consent, including the risks and benefits of ART, should be required.
- Ongoing longitudinal studies are necessary to fully understand ART outcomes.

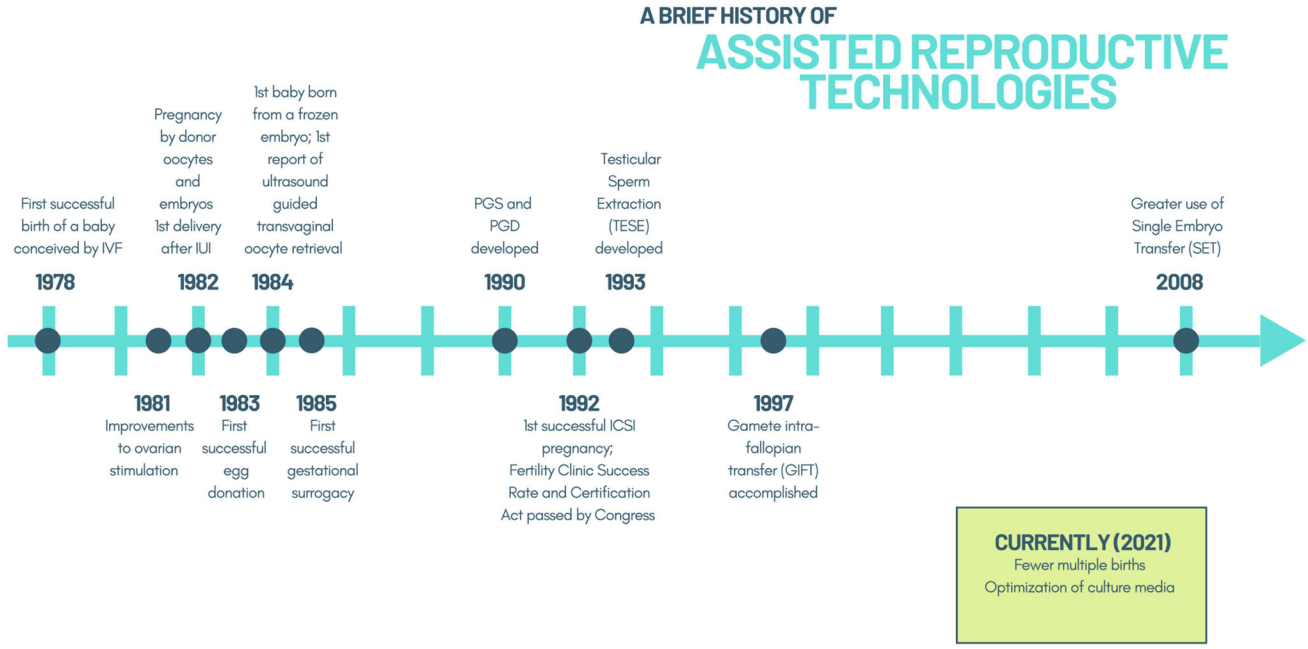

FIGURE 1.

A brief history of assisted reproductive technology (ART). Since the first live birth of an infant conceived by in vitro fertilization (IVF), ARTs have continued to evolve and advance.[9–12]

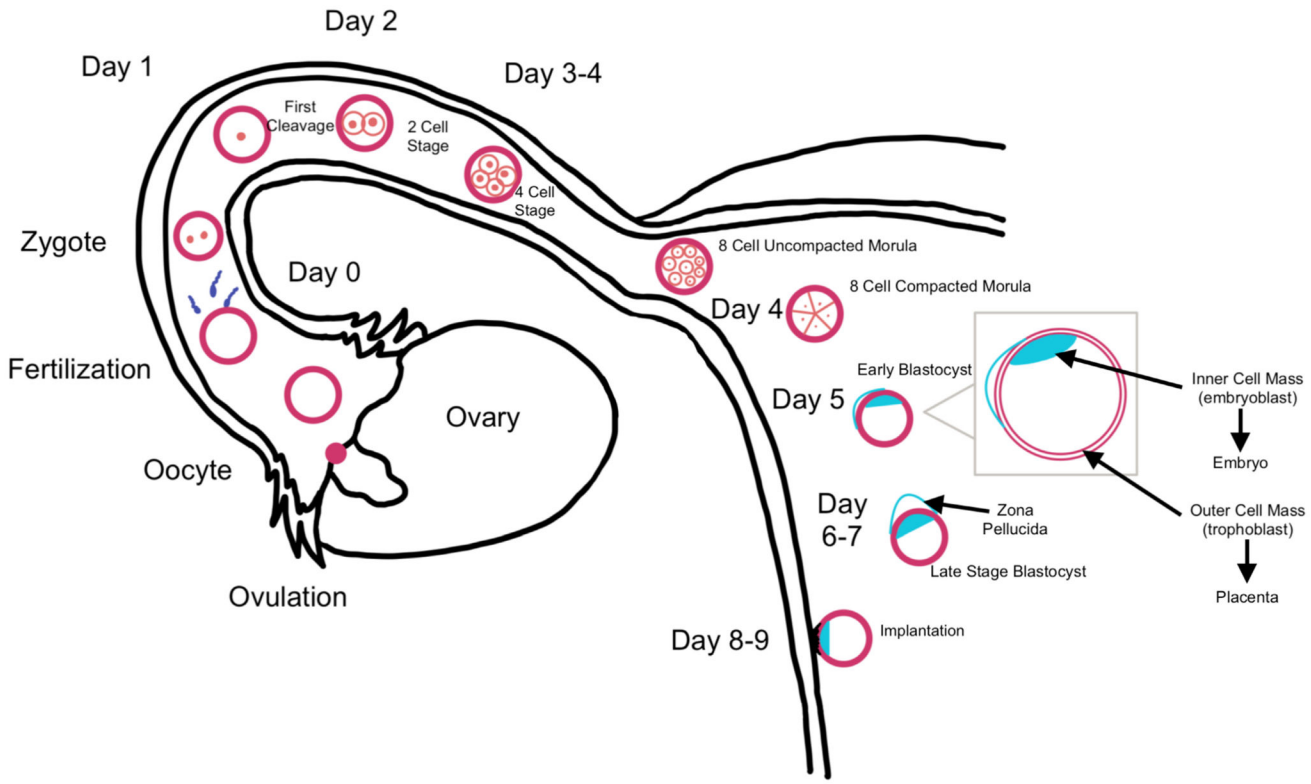

FIGURE 2.

Embryology. After ovulation and fertilization, the oocyte develops into a zygote which implants in the uterine wall. After implantation, the zygote will continue to develop until delivery.

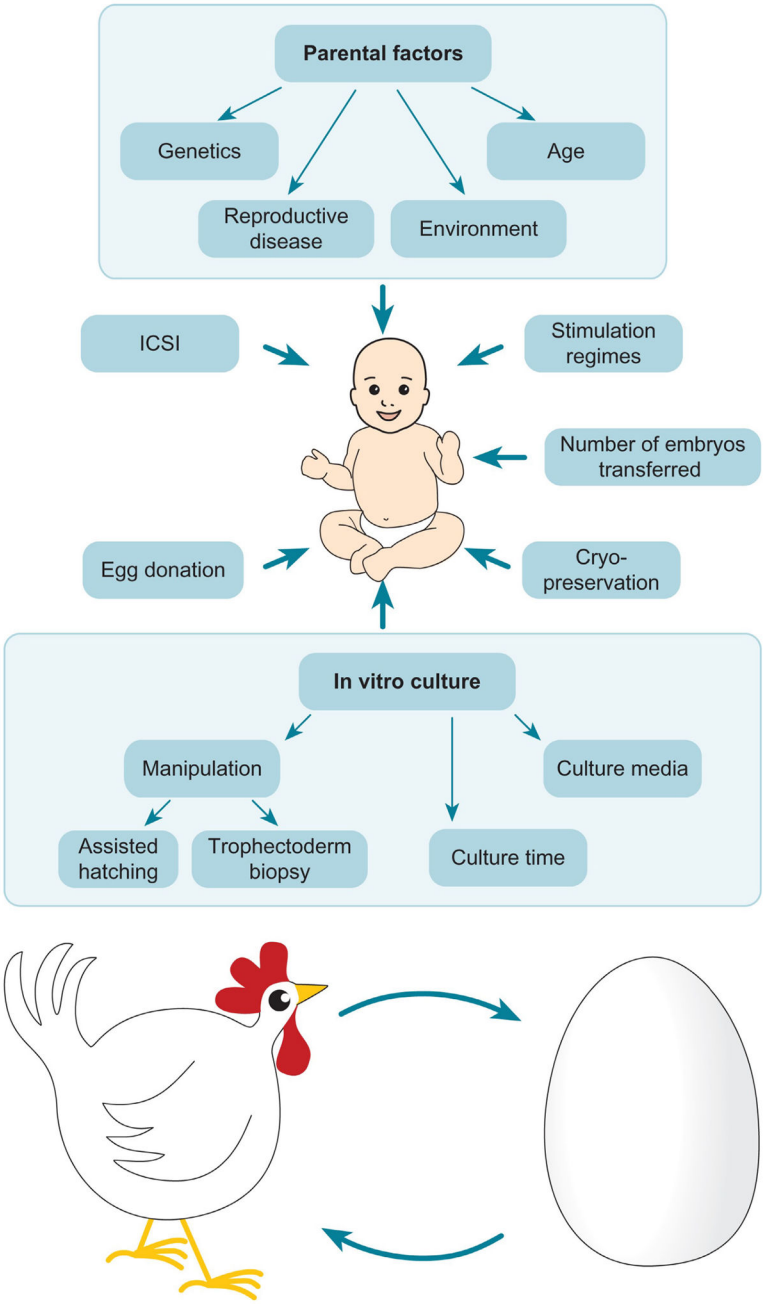

FIGURE 3.

A wide range of factors can adversely affect the offspring born after assisted reproductive technology. It is difficult to definitely determine the relationship between assisted reproductive technology and outcome. Reproduced with permission from Berntsen et al.[7]