The Assisted Reproductive Technologies Conceived Pregnancy: Pathophysiology, Risks, and Evolving Concepts

Authors:	Hüseyin Karakaya,[1] Gökhan Doğukan Akarsu[2] 1. Department of Gynecology and Obstetrics, Faculty of Medicine, Yozgat Bozok University, Türkiye 2. Department of Pharmacy Services, Vocational School of Health Services, Yozgat Bozok University, Türkiye *Correspondence to gokhan_dogukan_akarsu@hotmail.com

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Abstract

Assisted reproductive technologies (ART) have transformed infertility treatment from a medical intervention into a global standard of care. As the use of ART continues to expand worldwide, questions have emerged regarding whether pregnancies conceived through ART are biologically equivalent to those conceived naturally. Clinical evidence suggests that ART-conceived pregnancies are associated with increased risks of hypertensive disorders, placental complications, and gestational diabetes. However, it remains unclear whether these risks arise directly from ART procedures themselves or from characteristics commonly observed in the ART population, such as advanced maternal age and underlying metabolic disorders.

Specific ART practices, including frozen embryo transfer cycles performed without a corpus luteum and donor oocyte cycles, present unique hormonal and immunological challenges that may influence maternal adaptation to a genetically distinct embryo. Furthermore, laboratory conditions during the early stages of embryonic development have raised concerns regarding epigenetic modifications and their potential long-term health consequences. Although the majority of ART pregnancies result in healthy outcomes, growing evidence suggests that they may follow a distinct biological pathway. This perspective highlights the need for a more integrated, multidisciplinary follow-up approach aimed at optimising the long-term health and wellbeing of both mothers and their offspring.

Key Points

1. As the global use of assisted reproductive technologies (ART) continues to increase, understanding whether ART-conceived pregnancies represent a distinct obstetric phenotype has become increasingly important for maternal and offspring health.

2. This narrative review synthesises current evidence on the biological mechanisms, obstetric complications, epigenetic considerations, and long-term cardiovascular, metabolic, and psychological outcomes associated with ART pregnancies.

3. ART pregnancies should be managed using an integrated multidisciplinary approach, recognising their potential long-term maternal and offspring health implications while acknowledging that many risks also reflect underlying infertility-related factors.

INTRODUCTION

Over the past 40 years, assisted reproductive technologies (ART) have evolved into modern practices, influenced by shifts in experimental methodology. For an increasing number of people, ART is no longer just an alternative but is considered a realistic path to parenthood. In the modern world, the age of first-time mothers continues to rise, and societal pressures on fertility are increasing. Therefore, our reliance on these technologies is expected to increase.[1,2] However, the adoption of ART in society has changed the fundamental clinical debate. The goal is no longer simply to achieve a pregnancy. Instead, it is to examine the biological development of these pregnancies and whether they truly reflect the conditions of pregnancy occurring naturally. Large-scale observational studies have shown a higher risk of hypertensive disorders, placental problems, gestational diabetes, and altered fetal growth in ART-assisted pregnancies.[3,4] However, interpreting these data clearly is not easy. The ART population is inherently different from the general obstetric population. Advanced maternal age, metabolic dysfunction, endometriosis, and chronic inflammation diseases common in infertility cases influence the risk profile independently. This makes it difficult to separate the effects of ART from pregnancy development.

Rather than simple epidemiology, various biological theories are beginning to emerge. Successful implantation is not a solitary and independent outcome. It requires a perfectly timed interaction between embryo viability and endometrial receptivity. Potential disruptive factors being investigated include hormones above physiological levels during stimulation, altered corpus luteum (CL) function, changes in immune tolerance, and even epigenetic changes in the earliest stages of embryonic development.[5] At the same time, there are rapid advances in embryo selection and non-invasive diagnostic methods that are constantly being updated.[6]

Despite the breadth of existing literature, prior narrative reviews have largely examined individual risk domains such as preeclampsia, congenital anomalies, or epigenetic effects in isolation, without integrating the full spectrum of obstetric, metabolic, psychological, and long-term cardiovascular implications. This review adopts a broader, synthesising perspective, including the underappreciated but clinically significant issue of multiple gestations following ART, to provide a comprehensive biological appraisal of ART pregnancies as a distinct obstetric phenotype.

This raises a fundamental conceptual question: should we view ART pregnancies merely as an application for solving infertility treatment, or do they characterise a unique obstetric phenotype shaped by specific technological and hormonal effects? Answering this question is far from easy, but it is necessary to relate some insights to long-term maternal health. In the following sections, the authors evaluate whether ART pregnancies are a separate

biological issue, and in particular, their lasting effects on maternal cardiovascular health are assessed.

MATERIALS AND METHODS

This paper was conducted as a narrative review. A literature search was performed using PubMed/MEDLINE, Scopus, Web of Science, Cochrane Library, and Google Scholar databases. The search covered publications from 2018–2026. Only articles published in English were included. Search terms included combinations of the following: "assisted reproductive technology," "ART pregnancy," "preeclampsia," "placental dysfunction," "frozen embryo transfer," "congenital anomalies," "gestational diabetes," "cardiovascular outcomes," "epigenetics," and "embryo implantation." Relevant original research articles, systematic reviews, meta-analyses, and consensus statements were evaluated. Studies were selected based on their relevance to the clinical and biological aspects of ART pregnancies discussed in this review.

Placental Dysfunction and Hypertensive Disorders in ART Pregnancies

The most prominent and concerning obstetric complication associated with ART is preeclampsia.[7] While meta-analyses describe the overall increased risk as normal, its persistence across different populations keeps clinicians on alert. However, the real debate is not simply about the varying numbers. From this perspective, it concerns whether we are seeing a direct side effect of ART or a preexisting vulnerability in the patients themselves. Preeclampsia is fundamentally based on early placental dysfunction. For a pregnancy to develop, trophoblast invasion and the remodelling of the spiral arteries in the first critical weeks must be perfectly synchronised.

Even a small disruption in this early stage can impair later vascular adaptation. This raises the question: do ART pregnancies face a fundamentally different implantation environment from Day 1?

If we consider the hormonal mechanism, controlled ovarian stimulation fills the endometrium with oestradiol levels far beyond the natural level. Fresh embryo transfers occur in this hyperhormonal environment. Planned frozen embryo transfer cycles often take place without the CL. This is not just a technical detail. The CL produces vital molecules such as relaxin, which initiates early cardiovascular adaptation.[8] Without the CL, the body can compensate by endothelial remodelling, especially in women prone to cardiometabolic problems. However, research results show higher rates of hypertension in frozen embryo transfer cycles without the CL,[7] but we still need to account for other latent variables.

Donor egg pregnancies add another factor. Preeclampsia rates are consistently higher in ART pregnancies than in spontaneous pregnancies.[7] This cannot be attributed solely to hormones. It also involves the immune system. In the mother–fetus bond, natural killer cells and regulatory T cells in the uterus carefully balance tolerating the foreign embryo while protecting the mother.[9] In donor donations, where the genetic difference between mother and fetus is enormous, this immune tolerance is strained. This is a fascinating, yet flawed and incomplete clinical model for studying how a mother's body adapts to a genetic stranger. Nevertheless, caution is necessary. Women who enrol in ART are often older and have higher rates of experiencing metabolic comorbidities that independently increase their risk of high blood pressure.[10] This makes separating this effect from the patient's own biology a methodological ambiguity. The links are undeniable, but the definitive evidence is still unclear.

Early Pregnancy Loss, Implantation Biology, and Epigenetic Considerations

Despite significant advances in fertilisation and implantation rates, early pregnancy loss remains a persistent problem in ART. In the general population, more than half of early miscarriages are due to chromosomal abnormalities.[11] This is striking evidence that embryonic genomic integrity is the guardian of viability. Modern genomic tools

have reshaped our perspective on this issue. Big data analyses are now even more feasible. Thanks to triple exome sequencing and similar high-resolution techniques, previously invisible monogenic and structural variants are being revealed.[11-13] It is becoming clear that both sporadic and recurrent losses involve a complex genetic architecture where immune regulatory pathways and variants of rare and uncertain significance intersect.[13] In this sense, many ART related pregnancy losses explain an underlying biological vulnerability rather than a direct harm stemming from the ART stages themselves. Additionally, ART does not occur in a biological environment. The preimplantation environment is a carefully, albeit artificially, modulated space. Controlled hormonal stimulation can desynchronise the timing of embryonic and endometrial development. Even a small deviation during the implantation window can affect early stabilisation.[12]

Beyond hormones, there is growing interest in the genital microbiome. Changes in microbial composition can alter the strength of local inflammation and potentially shift the balance for or against a successful pregnancy.[5] The precise weight of this factor is still debated. This hypothesis is gaining significant importance.

Additionally, another layer is added to the epigenetic mystery. Early embryogenesis is a period of major DNA methylation and histone remodelling. It is a delicate stage interfered with by laboratory culture conditions.[14]

While overt suppression disorders remain rare, there are concerns that subtle regulatory changes may affect placental fertility or long-term metabolic health. Whether these molecular responses lead to meaningful clinical outcomes is one of the biggest unknowns.

Environmental factors also further complicate the picture. Endocrine disrupting chemicals have been reported to be linked to lower oocyte quality and altered development.[14,15] This situation is also considered to compromise sperm integrity.[16-18]

These external pressures make it difficult to distinguish between the innate biology of infertility and the effects of ART. Male factor infertility is also more complex than a standard sperm analysis suggests. Problems such as sperm DNA fragmentation and oxidative stress can silently undermine embryo viability.[19]

The rise of sperm selection suggests we are moving toward a more nuanced understanding, but whether these high-tech tools truly reduce obstetric risk in the long term has not yet been proven.[20]

Congenital Anomalies in ART Pregnancies: Signal, Bias, or Biological Effect

The debate about the link between ART and congenital anomalies is far from over. Several systematic reviews point to an increase in malformations in children conceived with ART. Congenital heart defects are frequently the focus.[20-22] Interpreting these data is quite difficult.

When researchers consider parental age, duration of infertility, and metabolic health status, this statistical correlation becomes intractable and does not yield a significant difference.[20,21] The dilemma arises again: does the technology itself create new risks, or does it accelerate their emergence in a population already predisposed to them?

From a biological perspective, ART procedures occur during a high-risk period of epigenetic reprogramming. While clinically significant genomic imprinting disorders are rare, scientists continue to study the more subtle epigenetic variations associated with ART procedures. Genomic imprinting refers to the epigenetic process by which certain genes are expressed in a parent-of-origin-specific manner, regulated primarily through DNA methylation. Disruption of this process can lead to well-defined clinical syndromes such as Beckwith–Wiedemann syndrome, Silver–Russell syndrome, Angelman syndrome, and Prader–Willi syndrome, which are characterised by growth abnormalities, neurodevelopmental

delay, endocrine dysfunction, and cancer predisposition. The frequency of some of these disorders is higher than expected in the general population following ART, and experimental evidence suggests that ART procedures may induce stress in the embryo and influence gene expression and DNA methylation patterns (particularly in imprinted regions) without producing global methylation alterations.[14,23]

There is also much debate about fresh and frozen embryo transfer protocols. However, so far, no approach has emerged as safer when it comes to the risk of congenital anomalies.

In a clinical setting, it is more important to discuss the absolute risk. Even if the relative risk appears statistically significant, the actual increase in the number of affected pregnancies is usually very small. The rise of non-invasive prenatal testing has completely changed the way we screen for these pregnancies.[6]

ART can provide earlier, more accurate diagnoses and personalised counselling, while also protecting patients from unnecessary invasive procedures.

Multiple Pregnancies Following ART: A Distinct Risk Category

Multiple gestation is one of the most significant and well-characterised complications of ART. The practice of transferring more than one embryo to improve cumulative live birth rates has historically driven a substantial increase in twin and higher-order pregnancies. Although elective single embryo transfer policies have reduced the frequency of multiples in many countries, multiple pregnancies continue to represent a disproportionate share of ART outcomes globally.

From a maternal perspective, multiple gestations markedly amplify the risks associated with singleton ART pregnancies. Rates of preeclampsia, gestational diabetes, peripartum haemorrhage, and Caesarean delivery are substantially higher in twin and triplet pregnancies.[24,25] The physiological demands of carrying multiple fetuses place greater strain on cardiovascular and metabolic systems already subject to the effects of infertility-related comorbidities and ART-specific endocrine exposures. Preterm labour is a near-universal concern: more than 50% of twin pregnancies deliver before 37 weeks of gestation, and higher-order multiples face even greater risks of extreme prematurity.[26]

For offspring, the consequences of multiple gestation extend well beyond the perinatal period. Low birthweight, intrauterine growth restriction, and neonatal intensive care admission are far more common in ART-conceived multiples than in singletons. Neurological and developmental sequelae associated with preterm birth, including cerebral palsy, cognitive impairment, and behavioural difficulties, are also elevated in this population.[24] Monochorionic twin complications, such as twin-to-twin transfusion syndrome, represent an additional source of perinatal morbidity specific to spontaneous or ART-related monozygotic twinning.

The promotion of elective single embryo transfer in clinical guidelines reflects a growing consensus that the optimal outcome of ART is a single healthy live birth. Wide adoption of this approach, supported by cumulative transfer strategies and improved cryopreservation techniques, has the potential to substantially reduce the burden of multiple pregnancy-related morbidity. Nonetheless, individual counselling remains essential, as the decision to transfer one or more embryos involves a complex negotiation of patient expectations, clinical circumstances, and evidence-based risk communication.

Metabolic, Psychological, and Long-Term Cardiovascular Implications

Studies have shown that gestational diabetes and hypertensive disorders are more common in women who conceive via ART.[7,10] Many patients undergoing ART already manage obesity, insulin resistance, or other components of metabolic syndrome. Each of these is a significant risk factor in itself.[10] In many cases, ART may not even be a trigger,

but rather a stage in which a pre-existing vulnerability emerges.

Furthermore, hypertensive disorders such as preeclampsia should no longer be dismissed as merely temporary complications of pregnancy. We must now consider them as early warning signs for future cardiovascular health. Studies show that women with a history of preeclampsia are at a much higher risk of chronic hypertension, ischaemic heart disease, and stroke later in life.[25] Whether ART accelerates this progression or merely intersects with it is still an open question. However, it is not a question with superficial clinical implications.

We must also not ignore the psychological aspect of these pregnancies. Conceiving after years of infertility treatment carries an emotional intensity rarely encountered in spontaneous pregnancies. The high-risk nature of pregnancy, the constant monitoring, and the persistent fear of loss create a unique stress profile.[24,26-28]

Qualitative studies describe a complex, often exhausting situation in these couples, characterised by overprotective behaviours and medical intervention.[29] While quantifying these factors is difficult, they are an integral part of the ART pregnancy phenotype.

Consequently, current evidence does not point to a single definitive cause. Instead, ART pregnancies are situated at a crossroads of biological predisposition, technology, endocrine changes, immune adaptation, and psychosocial factors. Rather than viewing ART as an isolated medical event, it is more accurate to see it as part of a lifelong reproductive and metabolic continuum. Adopting this broader perspective is the first and most important step towards a multidisciplinary approach that looks far beyond standard obstetric examination.

CONCLUSION

ART has fundamentally reshaped reproductive medicine, achieving results that seemed like science fiction 40 years ago. The undeniable evidence of this success lies in the millions of children born to families who had no path to parenthood. However, this clinical success does not mean we will not continue to ask more difficult, nuanced questions about biological adaptation and long-term safety. The data we have today show a consistent increase in risks such as hypertension, placental problems, certain congenital anomalies, and metabolic alterations. Importantly, these conditions are almost certainly not the result of a single factor. They represent a complex dialogue between the biology of infertility, parental health, artificial hormonal environments, immune tolerance, and the embryo's earliest environmental exposures. In the future, it is necessary to uncover the mechanisms behind these. Studies tracking lifelong cardiovascular, metabolic, and even psychosocial outcomes are needed. From this broader perspective, ART should be understood as more than just a tool used to achieve pregnancy. It will remain a critical stage in a woman's lifelong health journey.

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