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REVIEW

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IVF and pregnancy outcomes: the triumphs, challenges, and unanswered questions

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Abstract

Background In vitro fertilization (IVF) has become an integral component of reproductive medicine, providing a pathway to parenthood for infertile and sub-fertile couples. Currently, IVF accounts for approximately 2–5% of all births globally. Over the past decades, the field has witnessed substantial advancements, including changes in patient demographics, embryology techniques, pharmaceutical agents, and treatment protocols.

Methods This review examines the evolution of IVF, focusing on technological innovations and shifting patient profiles, particularly the increasing number of older women undergoing treatment.

Results While technological and clinical innovations have enhanced IVF success rates and safety, they have also contributed to a broader patient population, including women with pre-existing medical conditions. These divergent trends—improved treatment efficacy alongside growing medical complexity—have reshaped the clinical and public health risk profiles associated with IVF.

Conclusions Ongoing surveillance, comprehensive patient counseling, and appropriate regulatory oversight are essential to sustaining high-quality reproductive care in the context of a continually evolving IVF landscape.

Keywords IVF, Perinatal outcome, Maternal age, Obesity, Hypertensive disorders of pregnancy, Gestational diabetes, Preterm birth, Abnormal birth weight, Abnormal placentation, Imprinting disorders

Introduction

In the early days of in vitro fertilization (IVF), pregnancies were rare, and most patients were young women with tubal factor infertility. Over the years, technological advancements significantly improved IVF success rates and expanded its applications to address a wider range of infertility causes. At the same time, societal and cultural shifts led to delayed childbearing, increasing the number of women seeking fertility treatments at older ages. Between 1992 and 2019, the IVF birth rate quadrupled, the proportion of women aged 38 and older doubled, and the rate of single embryo transfers (eSET) increased seven-fold [1].

As IVF technology has advanced, success rates have significantly improved, and its clinical applications have expanded beyond tubal factor infertility to include male factor infertility, unexplained infertility, diminished ovarian reserve, and preimplantation genetic testing (PGT) for genetic screening. In response to the growing demand from older women seeking to conceive, innovators in the field introduced techniques such as oocyte and embryo vitrification and PGT to rule out aneuploidy (PGT-A), helping more women achieve live births. Consequently, IVF has become increasingly prevalent especially among women 35 years and older, with 1.5–5.9% of all births in developed countries now resulting from IVF treatments [2]. This growing proportion has significant implications for national healthcare systems, stemming from the unique patient population that needs IVF to conceive as

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well as potential direct implications of the technology on pregnancy outcomes.

One major impact of IVF-conceived pregnancies has been on neonatal intensive care unit (NICU) admissions and the long-term healthcare costs associated with prematurity. Historically, in an effort to improve pregnancy rates, clinicians often transferred multiple embryos, leading to high rates of multiple pregnancies, including high-order multiples. These pregnancies carry a substantial risk of complications, primarily preterm birth, which results in an increased need for prolonged neonatal care. Prematurity is also associated with long-term health challenges, such as cerebral palsy, visual and hearing impairments, and developmental delays, all of which require ongoing medical intervention.

The rising healthcare costs associated with premature births prompted policy changes, leading to the widespread implementation of elective single embryo transfer (eSET) policies. These policies dramatically reduced the financial burden on healthcare systems while maintaining successful pregnancy outcomes. In 2018, in the USA, IVF accounted for 2% of all live births but contributed to 5.1% of all preterm births, with 26.1% of IVF births being premature. The average cost of care for a premature neonate was estimated at $98,270, with costs ranging from $2,057 to over $2 million per infant. These figures highlight the significant economic and clinical impact of IVF on maternal and neonatal health services [3, 4].

The fundamental concept of in-vitro fertilization (IVF) has paved the way for oocyte donation and surrogacy, redefining traditional family structures. These advancements have enabled gay men, women born without a uterus, and postmenopausal women to conceive and have children, expanding reproductive possibilities beyond conventional norms.

The aging trend among IVF patients is expected to continue, driven by societal shifts and advancements in reproductive technologies. While the overall use of IVF has steadily increased since its inception, the rise in IVF pregnancies among women aged 40 and older has been significantly more pronounced. The widespread adoption of oocyte and embryo cryopreservation, oocyte donation, and Preimplantation Genetic Testing for Aneuploidy (PGT-A) has enabled more women in their fifth and sixth decades of life to conceive and give birth.

Although these technologies help reduce the risk of fetal aneuploidy, they also contribute to an increasing number of pregnancies in older mothers, who face a higher likelihood of age-related health complications that may affect both maternal and fetal outcomes. As a result, the prevalence of pregnancy-related morbidities, such as those discussed in this review, is likely to rise in the coming years.

In this article we will focus on some of the altered pregnancy outcomes associated with IVF births.

Detrimental effect of IVF on perinatal outcome

1. Patient characteristics

Numerous studies comparing IVF pregnancies to naturally conceived (NC) births highlight key demographic and health differences between the two patient populations. A recent large cohort study by Yu et al. examined the characteristics of IVF vs. NC patients, analyzing over two million singleton births[5]. The findings revealed that women who conceived via IVF were generally older (mean age 32.8 vs. 28.15 years), had lower parity (nulligravid: 90.97% vs. 67.37%), were more likely to undergo cesarean delivery (76.75% vs. 47.6%), and had a higher rate of preterm births (37% vs. 4.57%).

Other studies have reported a higher prevalence of obesity among IVF patients compared to those who conceived naturally [6, 7]. Similarly, a cohort study in Ontario, Canada found that IVF patients were older, more likely to be nulliparous, and had higher rates of chronic medical conditions, including hypertension and diabetes, compared to those who conceived naturally [8]. A recent retrospective study from Israel compared 544 IVF births to 544 naturally conceived (NC) births, each within the same women. The study included 292 women, with 53.7% having a prior NC pregnancy before their IVF-conceived birth.

Key pregnancy outcomes such as gestational age at birth, preterm birth (PTB) rate, small for gestational age (SGA) newborns, pregnancy-induced hypertension, instrumental delivery, and cesarean section rates were analyzed between the IVF and NC pregnancies. Apart from higher maternal age and slightly lower birth weight in the IVF group, all other outcome parameters were comparable between the two groups. These findings suggest that the underlying patient characteristics, rather than the IVF procedure itself, are the primary contributors to the higher risk of adverse pregnancy outcomes in IVF-conceived pregnancies.

Between 1975 and 2022, global obesity rates among women nearly tripled, rising from 6.6% to 18.5%. In the United States, 42.4% of adults were classified as obese in 2018. Obesity rates were highest among both men and women aged 40 to 59.

That same year, the prevalence of severe obesity in the U.S. reached 9.2%, with women aged 40 to 59 showing the highest rates at 11.5% [9]. The trend of older individuals seeking IVF treatment, coupled with a rising prevalence of obesity, is expected to persist in the coming years. The impact of pregnancy in this demographic on maternal and neonatal health will be discussed in subsequent sections of this review and should be carefully considered by healthcare providers and policymakers.

2. Hypertensive disorders of pregnancy

Several recently published meta-analyses examined the difference between the incidence of hypertensive disorders of pregnancy among IVF and natural pregnancies [10–12]. The meta-analysis by Chin et al, include 85 studies and examined the incidence of preeclampsia (PET) in several clinical settings [10]. The study found PET to be more common in IVF singleton pregnancies (OR 1.70,95% CI 1.60–1.80, multiple pregnancies (OR 1.34; 95% CI1.20–1.50. Pregnancies achieved following frozen embryo transfer (FETs) were associated with a higher risk for PTE (OR 1.74; 95% CI 1.58–1.92). However, FETs in which endometrial preparation was done in an artificial cycle (e.g. non-ovulatory as opposed to an ovulatory cycle) were associated with a significantly higher risk for PTE (RR 1.972 95% CI 1.59–2.441) highlighting the importance of the secretions of the corpus luteum in promoting normal placentation [11]. The group of patients that conceived after oocyte donation (OD) was identified as a particularly at-risk population for PTE, having the highest odds of PTE out of all groups analyzed. The risks of PTE and severe PTE was increased in OD pregnancies compared to NC pregnancies (pooled OR of all subgroups: 5.09, 95% CI: 4.29–6.04,and OR: 7.42, 95% CI: 4.64–11.88, respectively) likely due this patient population being older with a higher rate of obesity and chronic hypertension, as well as often incapable of ovulation and with a double sided lack of familiarity with the genetic composition of the embryo. This finding have promoted a change of practice to promot ovulatory endometrial preparation for FETs where possible and administration of Aspirin during pregnancy to reduce the risk for PTE [11].

Several recent meta-analyses have explored the incidence of hypertensive disorders of pregnancy in IVF versus naturally conceived pregnancies [10–12]. Among them, the meta-analysis by Chih et al. analyzed data from 85 studies, evaluating the risk of preeclampsia (PET) across various clinical settings[10].

The findings indicated that PET was more prevalent in singleton IVF pregnancies (OR 1.70; 95% CI 1.60–1.80) and multiple IVF pregnancies (OR 1.34; 95% CI 1.20–1.50). Additionally, pregnancies following frozen embryo transfer (FET) exhibited a significantly higher risk of PET (OR 1.74; 95% CI 1.58–1.92).

However, when endometrial preparation for FET was conducted in an artificial (non-ovulatory) cycle rather than an ovulatory cycle, the risk of PET increased substantially (RR 1.97; 95% CI 1.59–2.44) [11]. This underscores the crucial role of corpus luteum secretions in supporting normal placentation.

Among all groups analyzed, oocyte donation (OD) pregnancies were identified as the highest-risk population for PET. The risk of PET and severe PET was significantly elevated in OD pregnancies compared to naturally conceived (NC) pregnancies, with a pooled OR of 5.09 (95% CI: 4.29–6.04) for PET and 7.42 (95% CI: 4.64–11.88) for severe PET. This increased risk is likely due to advanced maternal age, higher rates of obesity and chronic hypertension, and the lack of preceding ovulation as well as maternal genetic and immunologic familiarity with the embryo [12].

These findings have led to changes in clinical practice, encouraging the use of ovulatory endometrial preparation for FETs whenever possible and the routine administration of aspirin during pregnancy to mitigate PET risk [11].

With the growing number of older patients conceiving via ART, a rise in hypertensive disorders of pregnancy is anticipated. Recommended strategies to reduce this risk include encouraging natural cycle frozen embryo transfers, reducing the incidence of multiple pregnancies, and prescribing aspirin throughout gestation. Although these approaches may help curb the trend to some extent, continued research and the development of targeted interventions will be crucial for managing hypertensive complications in this population. Consequently, preeclampsia (PET) and related hypertensive disorders will likely remain a significant concern for clinicians caring for patients who conceive through IVF in the coming years.

3. Gestational diabetes

Multiple studies have suggested an increased risk of gestational diabetes mellitus (GDM) in pregnancies conceived through in vitro fertilization (IVF). A nationwide Finnish study spanning 1998–2018 found that IVF pregnancies had higher odds of developing GDM (aOR 1.26, 95% CI 1.07–1.47), even after adjusting for potential confounders such as mater-

nal age, body mass index (BMI), smoking status, and multiple pregnancies [13].

Similarly, a meta-analysis covering 1978–2019 included 37 studies and nearly 2 million singleton pregnancies, of which 63,760 were conceived via IVF [14]. The findings confirmed a significantly increased risk of GDM in IVF pregnancies (RR 1.53, 95% CI 1.39–1.69), regardless of study type. However, the elevated risk was significant only in IVF pregnancies that did not use ICSI for fertilization and in fresh embryo transfers—a trend also observed in the Finnish study.

Women with polycystic ovarian syndrome (PCOS) often exhibit insulin resistance, which may predispose them to GDM. A study by Mills et al. [15] explored this association by analyzing data from the Healthcare Cost and Utilization Project Nationwide Inpatient Sample (HCUP-NIS) database (2004–2014). Among over 9 million births, 14,882 were from women with PCOS, who had a significantly higher likelihood of developing GDM (aOR 2.19, 95% CI 2.02–2.37), even after adjusting for age, race, income level, insurance type, obesity, IVF use, previous cesarean section, chronic hypertension, pregestational diabetes, thyroid disease, myasthenia gravis, smoking, and recreational drug use.

These findings underscore the importance of careful monitoring and management of GDM in IVF pregnancies, particularly in patients with PCOS and those undergoing fresh embryo transfers. As the average age of IVF patients continues to rise, along with the increasing prevalence of comorbidities such as obesity, impaired glucose tolerance, and diabetes, the risk of GDM in ART pregnancies is expected to increase in the future. Proactive strategies will be essential in mitigating this growing risk.

4. Preterm delivery

Multiple pregnancies, often resulting from the practice of transferring multiple embryos during IVF, remain the most common treatment-related complication associated with assisted reproductive technology (ART). Compared to singleton births, multiple pregnancies carry higher risks of adverse outcomes, including low birth weight, developmental disabilities, and an increased likelihood of surgical delivery [16]. However, the most concerning consequence is the significantly elevated risk of preterm birth (<37 weeks) and very preterm birth (<32 weeks), both of which are associated with short- and long-term morbidity and mortality.

Over the past few decades, the global incidence of multiple pregnancies following IVF has declined significantly. This reduction is largely due to improvements in cryopreservation techniques and the widespread adoption of elective single embryo transfer (eSET) policies, enforced by national regulatory bodies overseeing ART. Current guidelines recommend eSET of a euploid embryo for all patients, regardless of age, and for embryos of unknown ploidy in women 38 years or younger [17]. This shift has had a major impact on reducing preterm births associated with ART.

In the United States, the percentage of multiple births among ART-conceived infants declined from 53.1% in 2000 to 21.4% in 2018 [3]. Similarly, in the UK, the Human Fertilization and Embryology Authority (HFEA) set a national multiple birth rate target of <10%, which led to a reduction to 8% of all IVF births [18]. Comparable declines in multiple birth rates have been observed in Canada [19], Australia [20], and other countries worldwide.

Since multiple pregnancies significantly contribute to preterm births, their associated medical complications have placed a substantial burden on healthcare systems. In the U.S., the estimated societal cost of a single preterm birth in 2016 was $64,815, amounting to approximately $1.3 billion for 19,511 ART-conceived preterm infants born in 2018 [3]. Despite accounting for only 2–3% of all infants, multiple pregnancies represent 15–20% of all preterm births, with nearly 60% of twins born preterm and almost all higher-order multiples delivered before 37 weeks [21].

However, even singleton IVF pregnancies are at a higher risk of preterm birth compared to naturally conceived pregnancies. A large Chinese cohort study analyzing nearly 2 million singleton births found that the risk of preterm birth in singleton IVF pregnancies was slightly increased (RR 1.65, 95% CI 1.25–2.18). This risk declined over the study period (2008–2017) and was more strongly associated with frozen embryo transfer (FET), polycystic ovary syndrome (PCOS), and endometriosis. Notably, when controlling for preeclampsia (PET), the association between IVF and preterm birth was eliminated [5].

While the reduction in multiple pregnancies has contributed to a decline in preterm birth (PTB) rates, the absence of effective interventions to prevent PTB—combined with the gradual increase in maternal age—continues to make ART a significant risk factor for PTB. Both idiopathic preterm birth and medically induced preterm delivery due to severe preeclampsia (PTE) remain prevalent among ART pregnancies, highlighting the need for further research and targeted prevention strategies.

5. Birth weight

Understanding the impact of IVF on birth weight has evolved over time. Early studies indicated that IVF was linked to a higher incidence of low birth weight (LBW) (<2.5 kg) and very low birth weight (VLBW) (<1.5 kg). A study by Schieve et al.[22], which analyzed 42,463 IVF births alongside over 3.3 million naturally conceived (NC) births from 1996–1997, found that the risk of LBW was 2.6 times higher in IVF pregnancies. During that period, IVF accounted for only 0.6% of all births but contributed to 3.5% of all LBW cases and 4.3% of VLBW cases.

However, with advancements in cryopreservation techniques and improved pregnancy rates following frozen embryo transfer (FET), the use of FET cycles increased significantly. Over time, it became evident that FET-conceived births followed an opposite trend, showing a higher prevalence of large for gestational age (LGA) infants and macrosomia (>4 kg) [23]. Rephrased Description of Findings:

A study by Ageheim et al. [23] examined the growth patterns of embryos conceived through fresh embryo transfer (Fresh ET), frozen embryo transfer (FET), and natural conception (NC) [23].

In their article the authors show that IVF-conceived embryos exhibit an accelerated growth rate peaking at the early second trimester, potentially influenced by in vitro culture conditions. Following this peak, the growth rate declines, with a more pronounced reduction in fresh transfers, suggesting differences in placental function and development between the two procedures.

In fresh transfers, where the maternal environment is exposed to supraphysiologic estrogen levels, the placenta may have a reduced capacity to sustain fetal growth, likely due to suboptimal placentation. This diminished ability to meet fetal nutrient demands may contribute to the observed differences in growth trajectories between fresh ET and FET pregnancies.

Understanding the trends and associations in IVF births is further complicated by the evolving nature of patient demographics, treatment protocols, and laboratory techniques. These factors are not static but rather highly dynamic—with patients becoming older, the proportion of frozen embryo transfers (FET) increasing, and continuous advancements in culture media, blastocyst transfers, cryopreservation methods, incubators, and ovarian stimulation protocols.

A recent study by Shah et al. [24] analyzed birth weight trends in singleton autologous pregnancies conceived at a large U.S. fertility clinic between 1995 and 2019. The study, which included over 14,000 singleton live births (9,280 fresh and 5,140 frozen), revealed that birth weight (BW) trends were obscured by simultaneous opposing factors.

Findings showed a significant annual decline in BW and the incidence of large-for-gestational-age (LGA) infants, yet this trend was counterbalanced by a concurrent reduction in preterm births (PTB) and an increase in FET cycles, which were associated with an average birth weight increase of 150 grams.

According to the authors, the gradual decline in BW may be attributed to advancements in embryological techniques, including the introduction of vitrification, benchtop incubators, and single-step culture media, which have refined embryo culture conditions and potentially influenced fetal growth outcomes.

6. Abnormal placentation and placental abruption

It has long been suspected that placental development in assisted reproductive technology (ART) pregnancies may be compromised, contributing to adverse pregnancy outcomes such as preeclampsia (PTE) and small-for-gestational-age (SGA) infants. These complications have been linked to placental formation under supraphysiological estradiol levels or the absence of a functional corpus luteum, both of which are common in ART-conceived pregnancies.

A meta-analysis published in 2018 by Vermey et al. [25], which included 33 studies and data from 124,215 ART and over 6 million non-ART singleton pregnancies, highlighted an increased risk of several placental disorders in ART pregnancies. The study reported that ART pregnancies had a higher likelihood of developing placenta previa (OR 3.76, 95% CI 3.09–4.59), morbidly adherent placenta (OR 2.27, 95% CI 1.79–2.87), and placental abruption (OR 1.87, 95% CI 1.70–2.06) compared to spontaneously conceived (SC) pregnancies.

Additional studies have also provided strong evidence that IVF-conceived pregnancies carry a higher risk of placental abruption, a serious complication where the placenta prematurely separates from the uterine wall. A large cross-sectional study by Zhang et al. [26], analyzing data from 78 million U.S. deliveries between 2000 and 2019, found that placental abruption occurred in 17 per 1,000 hospital discharges in ART pregnancies, compared to 11 per 1,000 in spontaneous conceptions. After adjusting for confounding factors, ART pregnancies were associated with a 42% increased risk of placental abruption (adjusted odds ratio [aOR] 1.42, 95% CI 1.34–1.51).

These findings emphasize the importance of close monitoring and management of pregnancies conceived through ART, particularly concerning pla-

cental health and function, to mitigate the risks associated with placental complications.

7. Congenital malformations

Research consistently indicates that ART, particularly IVF and intracytoplasmic sperm injection (ICSI), is associated with an increased risk of congenital malformations (CMs) compared to natural conception. This heightened risk spans multiple organ systems, including cardiovascular, neurological, musculoskeletal, and gastrointestinal anomalies. Several meta-analyses have explored these associations, highlighting that ART-conceived infants have a significantly higher prevalence of birth defects than naturally conceived infants [27–30]. However, despite this observed increase, the absolute risk remains relatively low, with most anomalies being minor and not requiring medical intervention.

Among different ART methods, ICSI has been identified as carrying a slightly higher risk of specific congenital anomalies, particularly affecting the urogenital and musculoskeletal systems. The reasons behind this association remain uncertain but may involve epigenetic changes, sperm selection techniques, or underlying infertility-related factors. Some researchers suggest that male infertility itself, rather than the ICSI procedure, could be contributing to the increased risk of birth defects in ICSI-conceived infants. This underscores the need for further research to differentiate between the effects of the ART procedure and the genetic or epigenetic factors linked to infertility.

Maternal and paternal factors also appear to play a role in the increased incidence of congenital anomalies among ART pregnancies. Advanced maternal age, underlying infertility, and male factor infertility are all potential contributors to the elevated risk observed in these pregnancies. Some studies suggest that infertility itself, rather than ART procedures, may be partially responsible for the higher incidence of congenital malformations. However, due to variations in study design, population characteristics, and diagnostic criteria, direct comparisons between different studies remain challenging [27]. This highlights the importance of standardizing definitions of congenital anomalies and conducting long-term follow-up studies to assess developmental outcomes in ART-conceived children more accurately.

The clinical implications of these findings emphasize the need for enhanced prenatal screening and counseling for parents undergoing ART. Improved patient selection, optimization of embryo culture conditions, and a careful reconsideration of ICSI use in cases where it is not strictly necessary could help mitigate potential risks. While ART is associated with a slightly higher risk of congenital anomalies, most cases involve minor defects that do not significantly impact neonatal health. The ongoing development of ART techniques and a deeper understanding of the interplay between infertility, ART procedures, and congenital anomalies will be crucial in refining fertility treatments and ensuring better outcomes for ART-conceived children.

The increased accessibility and utilization of technologies such as Pre-Implantation Genetic Testing (PGT) for Aneuploidy and single-gene mutations is expected to lead to a decline in neonatal anomalies among IVF-conceived infants. In the future, the integration of gene-modifying technologies may further contribute to this trend. This technology is already feasible and has sporadically been used. The barrier for its widespread adoption remains concerns of regulatory bodies of misuse and potential unforeseen adverse effects that will be inherited to future generations. Additionally, the widespread use of ultrasound anatomical scans in all pregnancies has already improved the early detection and management of fetal anomalies before birth. However, recent legislative changes in both the USA and Europe may restrict the termination of affected pregnancies, potentially impacting how these conditions are addressed.

8. Imprinting disorders

In mammals, a subset of autosomal genes is exclusively expressed from one of the two parental chromosomes, with some being activated from the maternal allele and others from the paternal allele. This parent-of-origin-dependent gene expression arises due to differential epigenetic modifications, primarily through the methylation of cytosine residues at CpG dinucleotides, which occurs during gametogenesis in both male and female germlines. As a result, either the maternal or paternal allele of an imprinted gene is epigenetically silenced, leading to monoallelic expression. This selective regulation is essential for proper development, and any disruption can lead to genomic imprinting disorders.

These genomic imprints persist for one generation, from their establishment in the germ cells of an individual to their elimination in the gamete precursors of the next generation, making genomic imprinting a form of intergenerational epigenetic inheritance. In humans, approximately 100 imprinted genes have been identified, many of which play critical roles in embryonic and postnatal development. Disruptions in the expression or function of these genes can result in imprinting disorders, which are congenital

conditions with lifelong health consequences and, in some cases, an increased risk of cancer.

Several human disorders have been linked to abnormalities in genomic imprinting:

Prader-Willi Syndrome (PWS): Caused by the loss of expression of paternally inherited genes in the 15q11-13 region, PWS is characterized by hypotonia, obesity, hypogonadism, and intellectual disabilities. It is a rare condition, occurring in approximately 1 in 10,000 to 1 in 25,000 live births.

Angelman Syndrome (AS): Resulting from the absence of maternal gene expression in the same chromosomal region as PWS, AS is associated with epilepsy, tremors, and a persistently smiling facial expression. It is estimated to affect 1 in 12,000 to 1 in 20,000 individuals.

Beckwith-Wiedemann Syndrome (BWS): This disorder is linked to overgrowth and an increased risk of tumor development due to imprinting defects on chromosome 11p15. The incidence of BWS is approximately 1 in 13,700 live births.

Silver-Russell Syndrome (SRS): Associated with growth retardation and distinct dysmorphic features, SRS is caused by imprinting abnormalities on chromosomes 7 and 11. It is an extremely rare condition, occurring in approximately 1 in 100,000 live births.

Assisted reproductive technologies (ART), including IVF and intracytoplasmic sperm injection (ICSI), have been associated with an increased risk of certain imprinting disorders in offspring.

A comprehensive systematic review and meta-analysis by Lazaraviciute et al. [31] analyzed data from multiple studies comparing children conceived via IVF and ICSI to those conceived spontaneously. The findings indicated a higher incidence of imprinting disorders among ART-conceived children, with a combined odds ratio of 3.67 (95% CI: 1.39–9.74). However, the study found insufficient evidence linking ART to widespread methylation changes in other imprinted genes. The authors emphasized the need for more controlled studies with standardized methodologies to fully understand ART's impact on DNA methylation and imprinting.

A recent cohort study by Hattori et al. [32] analyzed data from a nationwide epidemiological study in Japan conducted in 2015. The researchers surveyed 2,777 pediatric departments across the country and identified 931 patients with imprinting disorders, including 111 cases of Beckwith-Wiedemann Syndrome (BWS), 227 cases of Angelman Syndrome (AS), 520 cases of Prader-Willi Syndrome (PWS), and 67 cases of Silver-Russell Syndrome (SRS). A significant proportion of these patients were conceived through IVF/ICSI and exhibited abnormal DNA methylation patterns at imprinted gene loci, particularly among those with SRS.

For BWS and SRS, the number of ART-conceived cases was 4.46 times and 8.91 times higher, respectively, than expected. Similarly, the number of PWS cases in ART pregnancies was 3.44 times higher than anticipated. However, no significant increase was observed in ART-conceived AS cases compared to expected rates. These findings, along with other studies, reinforce the association between ART and imprinting disorders.

Despite the exponential rise in ART use and the number of births from ART pregnancies, there has been no corresponding epidemic of imprinting disorders. This underscores the need for further investigation to determine the precise causal relationship and identify the specific components of ART procedures that may contribute to these epigenetic alterations. Understanding these mechanisms is crucial for refining ART techniques and minimizing potential risks.

9. Other poor obstetrical outcomes

Beyond the previously discussed adverse perinatal outcomes, several other obstetric complications have been linked to pregnancies conceived through ART. A large nationwide survey conducted in the United States, published in 2017 by Sabban et al., analyzed data from 5,773 IVF pregnancies between 2008 and 2011 and compared them to over 3 million naturally conceived pregnancies [7]. The study identified several additional complications associated with IVF pregnancies, including antepartum hemorrhage (OR 2.04, 95% CI 1.79–2.32), placenta previa (OR 3.14, 95% CI 2.71–3.64), preterm premature rupture of membranes (PPROM) (OR 1.49, 95% CI 1.30–1.70), chorioamnionitis (OR 1.52, 95% CI 1.29–1.79), and an increased likelihood of cesarean section (OR 1.60, 95% CI 1.51–1.70).

Postpartum complications were also significantly more common in IVF pregnancies, with higher rates of postpartum hemorrhage (OR 2.95, 95% CI 2.29–3.80), hysterectomy (OR 1.73, 95% CI 1.12–2.69), disseminated intravascular coagulation (OR 2.23, 95% CI 1.24–3.99), blood transfusion (OR 1.78, 95% CI 1.53–2.07), and prolonged hospitalization (OR 1.96, 95% CI 1.80–2.14). However, the IVF population was generally older and had higher rates of multiple pregnancies, which may have contributed to these findings.

A more recent retrospective study from China by Tai et al. [2] analyzed all births recorded at Nanjing Women's Hospital between 2011 and 2020, including 13,600 ART pregnancies and nearly 200,000 natural conceptions. The study also identified multiple obstetric complications

associated with ART pregnancies. However, since the ART cohort included a large proportion of multiple pregnancies, further analysis was conducted focusing exclusively on singleton pregnancies. When restricted to singletons, the following associations remained statistically significant:

- Gestational diabetes mellitus (GDM): OR 1.40 (95% CI 1.33–1.47)
- Preeclampsia (PTE): OR 1.27 (95% CI 1.12–1.43)
- Liver-related diseases: OR 1.17 (95% CI 1.04–1.30)
- Preterm birth (PTB): OR 1.64 (95% CI 1.49–1.80)
- Placenta previa: OR 1.46 (95% CI 1.35–1.58)
- Postpartum hemorrhage: OR 1.17 (95% CI 1.10–1.25)
- Cesarean section: OR 2.92 (95% CI 2.77–3.08)
- Stillbirth or abnormal fetal development: OR 3.48 (95% CI 3.01–4.03)

These findings reinforce the association between ART and an increased risk of obstetric complications, even when controlling for multiple gestations. While advancements in ART continue to improve pregnancy success rates, close monitoring and tailored clinical management remain essential to mitigate these risks.

Discussion

IVF has advanced significantly since its early days, driven by continuous innovation in pharmaceuticals, laboratory techniques, and treatment protocols. These advancements have steadily improved both the efficiency and safety of IVF, expanding its accessibility to patient populations who might otherwise have been unable to conceive. Among these are older women, who can now achieve pregnancy thanks to developments such as oocyte and embryo cryopreservation, preimplantation genetic testing for aneuploidy (PGT-A), and oocyte donation.

It is well established that the primary barrier to natural conception at advanced maternal age is the decline in both oocyte quality and quantity, rather than impaired endometrial receptivity [33]. Anecdotal case reports have even demonstrated that with the aid of modern assisted reproductive technologies, pregnancies are possible at virtually any age, including well after menopause. As a result, the upper limit for pregnancies achieved via IVF is no longer strictly dictated by a woman's biological capacity to conceive, but rather by institutional policies and regulatory guidelines. In the U.S. and several other countries, there is no formal upper age limit for embryo transfer when using previously cryopreserved oocytes, embryos, or donor eggs. However, most clinics impose their own upper limits, typically ranging from 51 to 55 years [34].

Research, such as the study by Ganer Herman et al. [35], suggests that perinatal outcomes in women conceiving naturally or via IVF may be comparable, highlighting that poorer outcomes in IVF pregnancies are largely attributable to the characteristics of the IVF patient population itself. IVF patients tend to be older and more likely to have obesity and chronic health conditions. Advancing maternal age is strongly associated with obesity [9] and a range of chronic diseases, including hypertension, impaired glucose tolerance, diabetes, cardiovascular disease, and reduced renal and pulmonary function [36].

Pregnancy imposes significant physiological demands, including substantial hemodynamic, respiratory, renal, metabolic, and endocrine changes, which may strain even young and healthy women. For example, cardiac output rises by approximately 40% by the third trimester and increases further during labor. Respiratory volumes, effort, and glomerular filtration rate are also markedly elevated [37]. In women aged 50 and older, these physiological stresses may present significant risks to both maternal and fetal health.

Moreover, dynamic testing methods intended to detect underlying health conditions, such as stress tests, thallium scans, and spirometry, fail to accurately replicate the extreme physiological changes induced by pregnancy. Consequently, the predictive value of normal pre-pregnancy functional tests for cardiac or pulmonary health remains uncertain. For instance, it is unclear whether a negative pregestational thallium-dipyridamole scan can reliably predict a pregnancy free of cardiac complications [38].

While advancements in ART have enabled older women to achieve pregnancy, progress in the areas of prenatal screening, prevention of obstetric complications, and management of conditions such as preeclampsia and preterm birth has not kept pace. As a result, despite improvements in the safety of modern IVF techniques, the trend of an aging and more medically complex IVF patient population—characterized by higher rates of obesity—suggests that IVF pregnancies will continue to carry an elevated risk of obstetric complications and adverse outcomes.

In the absence of parallel progress in mitigating these risks, and with the continued growth of this patient demographic, there is a pressing need for policymakers to develop clear guidelines. Such guidelines should establish appropriate age limits or health criteria to determine eligibility for ART-assisted pregnancies, ensuring both maternal and fetal safety.

Conclusion

Pregnancies conceived through assisted reproductive technology (ART) are associated with an increased risk of adverse pregnancy outcomes. A significant portion of this elevated risk can be attributed to the unique characteristics of ART patients, who are often older, have higher body weight, and may have underlying health conditions. Another major contributing factor is the higher incidence of multiple pregnancies in ART, which has led to regulatory policies mandating elective single embryo transfer (eSET) when appropriate to mitigate these risks.

However, even after adjusting for maternal characteristics and multiple gestations, ART pregnancies still exhibit a residual risk for several adverse perinatal outcomes. Identifying the specific components of ART treatment that contribute to these risks is essential. Further research into the causal mechanisms underlying these associations may help optimize ART protocols, ultimately reducing the risks for both mothers and their offspring while maintaining high success rates in fertility treatment.

Authors' contributions

YB and JS wrote the main manuscript.

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Competing interests

The authors declare no competing interests.

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