

Long-Term Effects of Assisted Reproductive Technologies on Offspring Health: Metabolic, Neurodevelopmental, Birth, and Epigenetic

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ABSTRACT

Assisted Reproductive Technology (ART) has proven to transform fertility treatments for individuals who find it difficult to conceive after multiple attempts. However, the health outcomes in children born via ART are yet to be discussed precisely. This narrative review aims to summarize outcomes observed in infants conceived through ART, including metabolic, neurodevelopmental, birth, and epigenetic outcomes, while attempting to narrow the differences in the current literature, suggesting a need for further analysis. This review was conducted with the assistance of peer-reviewed journals indexed in PubMed, Google Scholar, Wiley Online Library, and MDPI, encompassing articles published since 2010. Search items included combinations of “assisted reproductive technology,” “neurodevelopmental outcomes,” and “metabolic outcomes.” The articles considered comprise narrative reviews, cohort studies, meta-analyses, and systematic reviews, all in English. Studies were selected based on factors relevant to children born through ART. A potential relationship exists between ART procedures and various health outcomes observed in infants conceived, including metabolic disorders, cognitive outcomes, birth outcomes, and epigenetic outcomes. Amongst them, the most frequently reported ones include preterm birth and large-for-gestational-age. However, confounding perinatal or parental factors, such as age, genetics, and parents’ metabolic health, complicate causal explanations, and the current literature has yet to provide a clear overview of their contribution. ART is associated with long-lasting consequences, such as metabolic, neurodevelopmental, and birth outcomes. To understand the underlying mechanisms driving these effects and to determine whether parental and perinatal factors play a greater role, longitudinal studies are recommended.

Keywords: Assisted reproductive technology (ART); birth outcomes; epigenetic changes; metabolic outcomes; neurodevelopmental outcomes; parental factors; preterm birth.

INTRODUCTION

Infertility has reached a global prevalence of approximately 10%. Consequently, ART (Assisted Reproductive Technology) has emerged as a vital option since the first successful IVF in 1978 for people who fail to conceive despite multiple attempts. According to Sunderam and others, as of 2018, approximately 203,119 ART cycles were performed, resulting in 36.38% live births.¹

However, research suggests that children conceived via ART have a slightly higher risk of developing metabolic and neurodevelopmental disorders. This can lead to significant long-lasting effects, such as difficulties in language, speech, behavior, and memory, along with the increased risk of heart disease, stroke, and type 2 diabetes due to altered metabolism. Nevertheless, multiple studies have reported that the risk of similar neurodevelopmental outcomes in children born after infertility treatment is almost identical to that in naturally conceived ones, which indicates further analysis.

Although a link between ART and such outcomes is suggested, current findings are general and fragmented. Current literature highlights these outcomes, but distinguishing whether the complications arise from ART techniques (e.g., IVF, ICSI, FET) or due to underlying parental

factors (e.g., infertility, age) is necessary for enhancing clinical practices and counselling. This review aims to address these gaps by synthesizing recent findings and identifying emerging trends in the health outcomes of children conceived through ART.

REVIEW

Metabolic outcomes

Metabolic outcomes in ART-conceived children have been a subject of study, with findings highlighting elevated risks for various conditions such as foetal hypertrophy, preterm birth, and congenital malformations, which are more likely to affect ART-conceived twins, as discussed by Faa and others.² There has also been evidence of premature vascular aging, which further contributes to increasing the risk of arterial hypertension in adulthood.³

Pinborg et al. also reported potential long-term cardiovascular problems such as ischemic heart disease, cardiomyopathy, heart failure, and cerebrovascular diseases.⁴ Additionally, elevated BMI, BP, fasting blood glucose, fasting insulin, and homeostatic model assessment of insulin resistance (HOMA-IR) values specifically in children LGA from



0.4 to 9.9 years of age were observed by Zhang in their extensive prospective cohort study, including over 14,000 ART-conceived children.⁵ A decreased level of ApoA, which may further increase carotid intima-media thickness—a marker for early atherosclerosis—was also noted by Cui.⁶

Conversely, some suggested no significant differences in BP, heart rate, triglycerides, or insulin resistance between ART and naturally conceived children. However, slightly elevated levels of total HDL and LDL cholesterol were noted in ART offspring, particularly in adulthood, Elhakeem.⁷

Collectively, these studies indicate that ART-conceived children may face various cardiometabolic conditions, although whether they are caused by underlying parental factors or the specific ART procedures remains unclear.

Neurodevelopmental outcomes

Following metabolic outcomes, neurodevelopmental outcomes in these children are another significant challenge. Although widely studied, there have been varied and conflicting results. Faa and colleagues² highlight developmental delays chiefly in language and motor abilities. The risk is more pronounced in cases of multiple or premature births. Mild cognitive impairments and behavioural issues were observed in children conceived via ICSI by Pinborg and others.⁴ These concerns may be reinforced by the findings of Lo,⁸ which suggest a potential mechanism by which ICSI may bypass natural sperm selection and increase the risk of transmitting fragmented DNA. In a cohort study by Rönö,⁹ the increased risk of learning or motor disorders, ASD, ADHD, and conduction disorders was highlighted. Nonetheless, no significant difference was stated between the types of procedures used, such as IVF, ICSI, or FET. It is also worth mentioning that this risk was found to be amplified by anovulatory infertility or endometriosis.

In contrast, according to Farhi and others,¹⁰ there is no substantial difference in the long-term neurodevelopmental effects between ART and naturally conceived children. Zhu and colleagues¹¹ suggest that these outcomes may be more closely linked to perinatal and parental factors. Studies conducted by Balayla¹² indicate that children born via ART at two years of age had similar cognitive, motor, and language development as naturally conceived peers. Likewise, Wagenaar¹³ predicted no significant differences in information processing, attention, and visual-motor skills.

Overall, while some studies suggest potential neurodevelopmental challenges associated with ART, the evidence remains inconclusive. In the future, longitudinal research is needed to distinguish the consequences of ART

procedures from the underlying parental or perinatal factors. Follow-up studies on ART technique-specific effects can emphasize this.

Birth outcomes

Birth outcomes in children represent a significant category of discussion in children conceived via ART. Findings from Faa² highlight an elevated incidence of preterm birth and low birth weight, particularly among twins and multiple births from ART. Pinborg and others⁴ have highlighted the risks of being born large for gestational age (LGA) following frozen embryo transfers (FET). They added that even singletons born after ART carry higher obstetric and perinatal risks than spontaneously conceived ones. They further mention that both fresh and frozen embryo transfer singletons are more likely to be small for gestational age (SGA), have low birth weight, and be born preterm.

On the other hand, FET singletons are more often large for gestational age (LGA). Regarding childhood malignancies, conflicting evidence stating a possibly high risk in children born after FET vs spontaneous conception is noted. Moreover, as stated by them, ART offspring may face an increased risk of early onset puberty; in boys, the risk of late puberty also prevails.

According to Maheshwari et al.,¹⁴ Frozen embryo transfers (FETs) pose a lower risk of low birth weight (LBW) and very low birth weight (VLBW) compared to fresh transfers. However, FET was associated with an increased risk of high birth weight (>4 kg). Their study did not cite a significant difference in preterm or very preterm delivery rates between FET and fresh transfers.

Certain studies cite preventive strategies, such as Single Embryo Transfer (SET), which can reduce preterm and multiple birth rates and lower the risk of neurological impairments.¹⁵

Epigenetic outcomes

Epigenetic changes refer to modifications that affect gene activity and expression without altering the DNA sequence itself—often influenced by environmental factors, including early developmental conditions. Faa and others² highlight that their study raises concern about how ART techniques may interfere with normal epigenetic reprogramming. They also note several contributing factors, including hormonal stimulation and embryo freezing. Additionally, Frozen Embryo Transfer (FET) may affect epigenetic patterns, as suggested by Pinborg.⁴ These epigenetic alterations may contribute to the increased occurrence of large-for-gestational-age (LGA) births and macrosomia.

Scioria and peers¹⁶ have observed that KvDMR1 (an imprinting control region regulating growth-related genes on chromosome 11) is atypically methylated in ART-related Beckwith-Wiedemann Syndrome (BWS) and exhibits hypomethylation in ART-derived Bovine Conceptuses with LOS. There was no direct link found between PCOS or Angelman Syndrome (AS) with IVF and ICSI, but rather with underlying infertility issues themselves. Additionally, ovarian stimulation is reported to be a key driver of epigenetic aberrations in oocytes and embryos. DNA methylation errors in PEG1, KCNQ1OT1, and ZAC were found to be elevated in oocytes collected following controlled ovarian stimulation as compared to naturally conceived ones. Altered methylation at the H19 ICR in embryos from superovulated oocytes also supports this finding. While some normal ICR (imprinting control region) methylation patterns were still maintained in some mature oocytes, aberrations were detected in genes involved in glucose metabolism, nervous system development, mRNA processing, cell cycle, and proliferation. Moreover, multiple superovulation cycles resulted in adverse ovarian and embryo outcomes, aberrant histone modifications, and reduced fertilization rates.

Moreover, according to Lazaraviciute and others,¹⁷ there were no significant differences in cord blood DNA methylation of key genes (PEGs, IGF2, SNRPN, etc.), but in placentas, a lower DNA methylation at H19/IGF2, KCNQ1OT1, LINE1Hs, and ERVKRD1 in IVF/ ICSI than in control placentas. Additionally, placentas from ICSI (not IVF) have exhibited global differences in H3K4me3. Their findings regarding paternal epigenetic contributions also focused on the association between male obesity and paternal diet, as well as the resulting changes in the sperm epigenome. These changes are considered to be transmissible, especially via ART/ICSI. Additionally, it has been reported that abnormal histone acetylation in sperm leads to poor chromatin compaction and alteration, which can be transmitted to future offspring. Their findings additionally described that altered methylation at Alu repeats and imprints in sperm of infertile men are linked to ART outcomes. It is important to note that IVF culture under low oxygen improves outcomes, but embryo manipulations must be minimized.

A need for more rigorous evidence at the molecular level remains. Overall, while some studies focus on epigenetic changes, definitive conclusions remain to be drawn, as human evidence is limited, with most studies small-scale and short-term.

Perinatal and parental factors

Parental and perinatal characteristics majorly influence ART-related outcomes such as birth weight and preterm birth, suggesting an interplay of both ART procedures and these factors.² Pinborg,⁴ in their studies, emphasize the impact of frozen embryo transfer (FET) and maternal characteristics such as BMI and infertility etiology on birth outcomes. They suggest that outcomes such as LGA (large for gestational age) and macrosomia may be more closely associated with maternal metabolic factors than with ART itself. They also noted that multiple embryo transfer increased the risk of preterm birth and perinatal mortality even in singletons. No independent associations were found between parental/ART treatment factors and congenital anomalies. Interestingly, although differences in follicular fluid composition (e.g., VEGF, IGFs, and their binding proteins) were noted between GnRH agonist and antagonist stimulation, their effect on birth weight remains unclear, though potential epigenetic alterations cannot be excluded.

Pontesilli¹⁸ in their study mention that lower birth weight is associated with both parental characteristics (maternal hypertensive disease, diabetes, ethnicity, parity, and duration of subfertility) and ART treatment characteristics (HCG for luteal phase support, number of oocytes retrieved, and fresh vs. frozen embryo transfer). Maternal diabetes has been found to have the strongest association with low birth weight. Their study suggests that preterm birth is more common in South Asian mothers. These findings are further supported by recent comprehensive reviews highlighting increased preterm birth weight rates in ART-conceived children.

Collectively, these findings strengthen the argument that underlying parental and perinatal variables may largely explain many risks previously attributed to ART.

CONCLUSIONS

This review synthesizes findings across metabolic, neurodevelopmental, birth, and epigenetic outcomes in ART-conceived children. A range of outcomes, including cardiometabolic disorders, altered glucose metabolism, elevated blood pressure, various cardiovascular conditions, and birth outcomes, comprising low birth weight - particularly in twins, preterm birth, neonatal complications, and congenital malformations, were observed. Although a few findings across studies remain inconsistent, stating no substantial differences between ART and naturally conceived children.

A relationship between ART procedures and various perinatal and parental factors also contributes significantly. Perinatal risks such as prematurity may have long-term effects.

Additionally, parental factors, including maternal age and education, also contribute significantly.

Despite the extensive research findings, limitations such as the use of different ART procedures, small sample sizes, and short follow-up durations exist. Although this review synthesizes large-scale trends and outcomes, the underlying biological mechanisms remain a vital area for future investigation. For example, altered methylation patterns, oxidative stress during critical periods of embryo culture, and hormonal influences during controlled ovarian stimulation have been considered as potential intermediaries for observed outcomes.

From a clinical perspective, these studies highlight the importance of long-term pediatric follow-up and early screening for children born via ART. Along with providing supportive reproductive decisions, it will also promote brighter future reproductive practices, as well as improve the outcomes for children conceived through ART.

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REFERENCES

1. Sunderam S; Kissin DM; Zhang Y; Jewett A; Boulet SL; Warner L; Kroelinger CD; Barfield WD. Assisted reproductive technology surveillance — United States, 2018. *MMWR Surveill Summ.* 2022;71(4):1–19. doi:10.15585/mmwr.ss7104a1.
2. Faa G, Manchia M, Fanos V. Assisted reproductive technologies: a new player in the foetal programming of childhood and adult diseases? *Pediatr Rep.* 2024;16(2):329–338. doi:10.3390/pediatric16020029.
3. Graham ME; Jelin A; Hoon AH Jr; Wilms Floet AM; Levey E; Graham EM. Assisted reproductive technology: short- and long-term outcomes. *Dev Med Child Neurol.* 2023;65(1):38–49. doi:10.1111/dmcn.15332
4. Pinborg A, Wennerholm UB, Bergh C. Long-term outcomes for children conceived by assisted reproductive technology. *Fertil Steril.* 2023;120(3 Pt 1):449–456. doi:10.1016/j.fertnstert.2023.04.022.
5. Zhang Y; Dai K; Chen X; Cui L; Chen ZJ. Association between being large for gestational age and cardiovascular metabolic health in children conceived from assisted reproductive technology: a prospective cohort study. *BMC Med.* 2024;22:203. doi:10.1186/s12916-024-03419-7.
6. Cui L; Zhou W; Xi B; Ma J; Hu J; Fang M; Hu K; Qin Y; You L; Cao Y; Yang L; Yang L; Ma C; Shui W; Wang M; Zhao M; Zhang J; Chen ZJ. Increased risk of metabolic dysfunction in children conceived by assisted reproductive technology. *Diabetologia.* 2020;63:2150–2157. doi:10.1007/s00125-020-05241-1.
7. Elhakeem A; Taylor AE; Inskip HM; Huang JY; Mansell T; Rodrigues C; Asta F; Blaauwendraad SM; Håberg SE; Halliday J; Harskamp-van Ginkel MW; He JR; Jaddoe VVW; Lewis S; Maher GM; Manios Y; McCarthy FP; Reiss IKM; Rusconi F; Salika T; Tafflet M; Qiu X; Åsvold BO; Burgner D; Chan JKY; Gagliardi L; Gaillard R; Heude B; Magnus MC; Moschonis G; Murray D; Nelson SM; Porta D; Saffery R; Barros H; Eriksson JG; Vrijkotte TGM; Lawlor DA. Long-term cardiometabolic health in people born after assisted reproductive technology: a multi-cohort analysis. *Eur Heart J.* 2023;44(16):1464–1473. doi:10.1093/eurheartj/ehac726.
8. Lo H, Weng SF, Tsai EM. Neurodevelopmental disorders in offspring conceived via in vitro fertilization vs intracytoplasmic sperm injection. *JAMA Netw Open.* 2022;5(12):e2248141. doi:10.1001/jamanetworkopen.2022.48141.
9. Rönö K; Rissanen E; Bergh C; Wennerholm UB; Opdahl S; Romundstad LB; Henningsen AKA; Spangmose AL; Pinborg A; Gissler M; Tiitinen A. The neurodevelopmental morbidity of children born after assisted reproductive technology: a Nordic register study. *Fertil Steril.* 2022;117(5):1026–1037. doi:10.1016/j.fertnstert.2022.01.010.
10. Farhi A; Glasser S; Gabis LV; Hirsh-Yechezkel G; Frank S; Brinton L; Scoccia B; Ron-El R; Orvieto R; Lerner-Geva L. How are they doing? Neurodevelopmental outcomes at school age of children born following assisted reproductive treatments. *J Dev Behav Pediatr.* 2021;36(4):303–309. doi:10.1177/0883073820967169.
11. Zhu JL; Obel C; Basso O; Henriksen TB; Bech BH; Hvidtjørn D; Olsen J. Infertility, infertility treatment and behavioural problems in the offspring. *Paediatr Perinat Epidemiol.* 2011;25(5):466–477. doi:10.1111/j.1365-3016.2011.01220.x.
12. Balayla J; Sheehy O; Fraser WD; Séguin JR; Trasler J; Monnier P; MacLeod AA; Simard MN; Muckle G; Bérard A. Neurodevelopmental outcomes after assisted reproductive technologies. *Obstet Gynecol.* 2017;129(2):265–272. doi:10.1097/AOG.0000000000001837.
13. Wagenaar K; van Weissenbruch MM; Knol DL; Cohen-Kettenis PT; Delemarre-van de Waal HA; Huisman J. Behavior and socioemotional functioning in 9–18-year-old children born after in vitro fertilization. *Fertil Steril.* 2009;92(6):1907–1914. doi:10.1016/j.fertnstert.2008.09.026.
14. Maheshwari A, Raja EA, Bhattacharya S. Obstetric and perinatal outcomes after either fresh or thawed frozen embryo transfer: an analysis of 112,432 singleton pregnancies. *Fertil Steril.* 2016;106(7):1703–1708. doi:10.1016/j.fertnstert.2016.08.027.
15. Fouks Y, Yogev Y. Twinning in ART: single embryo transfer policy. *Best Pract Res Clin Obstet Gynaecol.* 2022;84:88–95. doi:10.1016/j.bpobgyn.2022.03.010.
16. Sciorio R, El Hajj N. Epigenetic risks of medically assisted reproduction. *J Clin Med.* 2022;11(8):2151. doi:10.3390/jcm11082151.
17. Lazaraviciute G; Kauser M; Bhattacharya S; Haggarty P; Bhattacharya S. A systematic review and meta-analysis of DNA methylation levels and imprinting disorders in children conceived by IVF/ICSI compared with children conceived spontaneously. *Hum Reprod Update.* 2014;20(6):840–852. doi:10.1093/humupd/dmu033.
18. Pontesilli M; Hof MH; Ravelli ACJ; van Altena AJ; Soufan AT; Mol BW; Kostelink EH; Slappendel E; Consten D; Cantineau AEP; van der Westerlaken LAJ; van Inzen W; Dumoulin JCM; Ramos L; Baart EB; Broekmans FJM; Rijnders PM; Curfs MHJM; Mastenbroek S; Repping S; Roseboom TJ; Painter RC. Effect of parental and ART treatment characteristics on perinatal outcomes. *Hum Reprod.* 2021;36(6):1640–1665. doi:10.1093/humrep/deab008.