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Long-Term Neurodevelopmental, Mental, and Cardiometabolic Health in Individuals Conceived with Assisted Reproductive Technology: A Literature Review

Saadia Ghafoor

Abstract—Background: **Assisted reproductive technology (ART) has revolutionised fertility treatments since 1978 and, while its immediate perinatal outcomes have been extensively studied, its long-term health effects require exploration.**

Method: **PubMed database was searched for studies spanning 2016 to 2023 to conduct this literature review of the long-term neurodevelopmental, mental, and cardiometabolic health of ART-conceived individuals.**

Results: **A total of 49 studies were included in this review. ART-conceived individuals revealed mostly positive neurodevelopmental and mental health impacts. However, children conceived via intracytoplasmic sperm injection (ICSI) demonstrated an increased risk of neurodevelopmental disorders, including autism spectrum disorder, intellectual disability, and psychological and neurological development delays, while frozen embryo transfer was linked to an increased risk of language delay. Additionally, children born via ART as multiples or prematurely showed an elevated risk of cerebral palsy. While ART generally demonstrated a favourable impact on cardiometabolic health, there were concerns about increased risk of high blood pressure, altered lipid profiles, obesity, insulin resistance, premature vascular aging, and adverse metabolic changes. Specifically, ICSI-conceived individuals were more prone to adiposity and insulin resistance, while frozen embryo transfer was associated with type 1 diabetes.**

Conclusion: **While ART-conceived individuals generally exhibit favourable health, specific subgroups may face elevated risks for certain neurodevelopmental disorders and long-term cardiometabolic issues, warranting further research. ART may be associated with metabolic alterations at a young age, potentially increasing the risk of chronic diseases such as metabolic syndrome, type 2 diabetes, and cardiovascular disease later in life. Continued long-term monitoring and targeted interventions are recommended to mitigate these risks.**

Index Terms— **Cardiovascular Diseases; Mental Health; Metabolic Syndrome; Neurodevelopmental Disorders; Reproductive Techniques "Assisted/Adverse Effects"; Risks.**

I. INTRODUCTION

Assisted reproductive technology (ART) has transformed fertility treatment since the first successful live birth through in-vitro fertilisation (IVF) in 1978. Assisted reproductive techniques account for over 4% of all live births [1]. Globally, ART has facilitated the birth of approximately 9 million babies, providing hope to countless infertile and subfertile couples [2]. ART encompasses various procedures designed to assist conception, with IVF being the most widely practiced. IVF involves fertilising an egg outside the body and transferring the embryo to the uterus. Another ART procedure, introduced in 1992, is the intracytoplasmic sperm injection (ICSI), which utilises a micromanipulation technique to pick up a single spermatozoan under the microscope and inject it into the oocyte using a micropipette. ICSI is useful in couples struggling with male infertility factors and a

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history of prior fertilisation failure or poor treatment outcome from previous IVF [3].

The World Health Organization's global report, 'Infertility Prevalence Estimates, 1990-2021', reveals that approximately one in six individuals worldwide experience infertility during their lifetime [4]. Other research highlights the considerable negative impact of advanced maternal age on fertility outcomes [5]. Similarly, findings by Alharbi et al. indicate that advanced paternal age can moderately affect certain semen parameters, further contributing to fertility challenges [6]. While assisted reproductive technologies have led to significant advancements in reproductive medicine, these procedures are associated with various health risks that must be carefully considered. Research has linked ART with adverse perinatal outcomes, such as preterm birth, low birth weight, and pregnancy-related complications; however, the exact cause remains uncertain [7], [8], [9]. Similarly, ART has been associated with an elevated risk of imprinting disorders and major non-chromosomal birth defects [10], [11]. While the birth defect risk among ART children is declining [12], the underlying mechanism for these associations is not known. There are concerns about the potential long-term health risks in ART individuals; however, the limited availability of data beyond early adulthood remains a challenge [13]. Despite extensive research into perinatal outcomes, significant gaps remain in our understanding of the long-term health risks, particularly regarding neurodevelopmental, mental, and cardiometabolic health in individuals conceived through ART. Although a substantial body of literature has examined its effects, the findings are often conflicting or inconclusive. This gap can significantly impact treatment decisions for couples struggling with infertility, making it essential to synthesise and critically evaluate the existing evidence. This literature review aims to address this knowledge gap in reproductive medicine by examining the topic and exploring the relevant research. The following sections of this review will explore and discuss the specific long-term health impacts associated with ART, focusing on neurodevelopmental, mental, and cardiometabolic health.

II. METHODOLOGY

This literature review conducted a detailed examination of the neurodevelopmental, mental, and cardiometabolic health-related impacts on individuals conceived through assisted reproductive technologies (ART), with a focus on synthesising and analysing research evidence from studies published between 2016 and 2023. The primary method for data collection involved a comprehensive literature search using the PubMed electronic database, targeting studies on the long-term effects of ART on neurodevelopmental, mental, and cardiometabolic health. The search strategy utilised MeSH terms combined with Boolean operators for precise filtering, applied as follows: for neurodevelopmental and mental health impacts, the MeSH terms included 'reproductive techniques, assisted/adverse effects', 'neurodevelopmental disorders', 'mental health', 'risks'; for cardiometabolic health impacts, the MeSH terms were 'reproductive techniques, assisted/adverse effects', 'cardiovascular diseases', 'metabolic syndrome', 'risks'.

Additional alternative search terms were employed in PubMed's Advanced Search Builder to broaden the scope of the search. Furthermore, reference lists from relevant studies published between 2016 and 2023 were meticulously reviewed to identify further research not initially captured. The search was continuously updated, with the most recent update on May 29, 2023. The inclusion criteria focused strictly on research explicitly related to the long-term effects

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of ART on neurodevelopmental, mental, and cardiometabolic health. Only studies published in English or those available in translated versions were considered. The exclusion criteria eliminated publications related to intrauterine insemination and other fertility treatments not classified as ART, as well as duplicate studies.

III. RESULTS

A total of 49 studies met the inclusion criteria and were included in the review, with 31 studies examining the neurodevelopmental and mental health-related impacts of ART, and 18 studies exploring the cardiometabolic health-related impacts.

Impact of ART on neurodevelopmental and mental health in ART-conceived individuals:

A total of 31 research studies included in this literature review explored the impact of ART on neurodevelopmental and mental health in ART-conceived individuals. The findings from the relevant studies have been organised into favourable findings, presented in Table 1, and adverse findings, in Table 2.

Table 1. Favourable Research Findings on Neurodevelopmental and Mental Health in ART-Conceived Individuals.

SN	Author, Ref. & Year of Publication	Favourable Research Findings on Neurodevelopmental and Mental Health in ART-Conceived Individuals
1	Li et al.[14] (2023)	Comparable language, motor, adaptive behaviour skills, and total development quotient scores in ART-conceived offspring compared with naturally conceived children at 12 months of age; slightly higher social development in ART male offspring and singletons.
2	Perros et al.[1] (2022)	Most literature shows no association between ART and poorer neurodevelopmental outcomes in offspring. The small number of studies suggesting possible associations between ART and neurodevelopmental disorders should be interpreted with caution in the presence of confounding factors. (The literature on these associations presents mixed findings.)
3	Fine et al.[15] (2022)	Lowest rates of diagnosed ADHD in children conceived via IVF/ICSI compared with other conception groups (unassisted conception, infertility without treatment, ovulation induction or intrauterine insemination). However, they exhibited slightly higher adjusted hazard ratios for ADHD.
4	Magnus et al.[16] (2022)	No added risk of neurodevelopmental delays or difficulties in ART-conceived children compared with naturally conceived children of parents with subfecundity. Parental subfecundity itself is linked to such delays.
5	Wei et al.[17] (2022)	No increased risk of hospitalisation for cerebral palsy, cognitive and motor development, and ASD in ART-conceived children after adjusting for shared genetic, environmental, and familial factors up to 11 years of age.
6	Roychoudhury et al.[18] (2021)	Preterm ART infants born at less than 29 gestational weeks have lower odds of adverse neurodevelopmental outcomes (particularly related to cognitive and language development) at 18 to 24 months corrected age compared with those conceived naturally.
7	Farhi et al.[19] (2021)	No significant difference in verbal skills, cognitive function, visual-motor ability, and attention between ART-conceived children and spontaneously conceived children of early school age.
8	Sánchez-Soler et al.[20]	No difference in neurodevelopmental disorders (autism spectrum, language delay, global developmental delay) in ART-conceived children (up

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	(2020)	to 3 years) compared with the control group after adjusting results according to specific confounders.
9	Jenabi et al. [21] (2020)	No significant association between ART and risk of ASD among children.
10	Bergh and Wennerholm[22] (2020)	No increased risk of delayed neurocognitive development or ASD after adjusting for multiple births in ART-conceived children (as identified by most studies)
11	Diop et al.[23] (2019)	No evidence suggests that singleton children born to ART/IVF/ICSI/subfertile women have a higher likelihood of ASD diagnosis during their first three years of life than children born to fertile women.
12	Mintjens et al. [24] (2019)	No statistically significant differences in neurodevelopmental or physical health among children conceived via in-vitro procedures of assisted reproduction and natural conception at a mean age of 5.5 years. However, the study's limited power and attrition could have obscured the detection of subtle effects.
13	Catford et al.[25] (2018)	Similar neurodevelopment, growth, vision, and hearing in children conceived by ICSI and natural conception (beyond the neonatal period).
14	Lung et al.[26] (2018)	No association between ART and ASD.
15	Davidovitch et al.[27] (2018)	No significant association between IVF treatment and ASD risk when compared with spontaneous conception.
16	Balayla et al.[28] (2017)	Similar neurodevelopment-related outcomes (including language, cognitive, and motor development) in children at age 2 conceived by ART and natural conception.
17	Klausen et al.[29] (2017)	No increased risk of adverse mental outcomes in children after ART exposure (during follow-up in childhood, adolescence, or early adulthood); study's power was limited to rule out ART's effect on specific mental health disorders.
18	Punamäki et al. [30] (2016)	No overall differences in mental health or social and cognitive developmental problems in ART children at 7 to 8 years compared with naturally conceived peers, although some gender-specific differences were observed.

ART: Assisted Reproductive Technology; ASD: Autism Spectrum Disorder; ADHD: Attention-Deficit/Hyperactivity Disorder.

Table 2. Adverse Research Findings on Neurodevelopmental and Mental Health in ART-Conceived Individuals.

SN	Author, Ref. & Year of Publication	Adverse Research Findings on Neurodevelopmental and Mental Health in ART-Conceived Individuals
1	Acharyya et al.[31] (2023)	Delayed growth and neurodevelopment in early infancy in term singleton babies conceived through ART compared with naturally conceived babies, but no statistically significant difference in outcomes at 24 months.
2	Rönö et al.[32] (2022)	Higher adjusted risk of learning and motor functioning disorders, and a tendency for higher risk of ASD, ADHD, and conduct disorders in ART singletons compared to non-ART singletons; only small differences in neu-

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		rodevelopment between ART and non-ART singletons; no difference in tic disorders risk after adjustment.
3	Fine et al.[15] (2022)	Children conceived via IVF/ICSI exhibited slightly higher adjusted hazard ratios for ADHD.
4	Wang et al.[33] (2021)	More than a two-fold increased risk of CP in ART children (mostly mediated by multiple and preterm births).
5	Sánchez-Soler et al.[20] (2020)	Association between language delay and FET observed in ART-conceived children (further research warranted).
6	Djuwantono et al.[34] (2020)	Higher CP risk in ART children than naturally conceived children, influenced by preterm birth and low birth weight; ICSI children face higher risks of intellectual disability and ASD than those conceived via conventional IVF; no significant difference in neurodevelopmental disorder risk between children born after frozen versus fresh embryo transfer.
7	Robinson et al.[35] (2020)	Toddlers conceived through ART may have increased chances of failing an ASD screening compared with those born without infertility treatment, though results remain inconclusive.
8	Rissanen et al.[36] (2020)	Slightly elevated risk of psychiatric diagnosis in children conceived through ART until young adulthood, compared with the control group.
9	Rumbold et al.[37] (2019)	A small increase in the risk of mental retardation and autism in ICSI-conceived offspring, suggesting that both severe male factor infertility and the use of ICSI may contribute, with inconsistent findings about the relative contribution of these factors.
10	Briana and Malamitsi-Puchner[38] (2019)	Neurodevelopmental outcomes in IVF-conceived twins are influenced by foetal growth restriction, prematurity, and zygosity, with higher CP in term infants, those with growth restrictions, prematurity, and twins surviving co-twin intrauterine death. The impact of IVF on these outcomes has not been documented, therefore warranting further research.
11	Esteves et al.[39] (2018)	Higher risk of delayed psychological and neurological development in infants born through ICSI than in children conceived naturally.
12	Goldsmith et al.[40] (2018)	A two-fold increase in the birth prevalence of CP after ART (mostly mediated by multiple and preterm births).
13	Liu et al.[41] (2017)	ART associated with a significantly higher risk of ASD in offspring, suggesting ART as an independent risk factor for ASD. (Caution is advised when interpreting the findings of this study.)
14	Kuiper et al.[42] (2017)	Less favourable health and development (lower total IQ, body weight, and height) in 4-year-old IVF twins than in 4-year-old IVF singletons, and not altered by IVF per se.
15	Xu et al.[43] (2017)	Reduced IQ in young children of OHSS IVF women compared with non-OHSS IVF children, potentially due to prenatal estradiol exposure.

ART: Assisted Reproductive Technology; ASD: Autism Spectrum Disorder; ADHD: Attention-Deficit/Hyperactivity Disorder; CP: Cerebral Palsy; IQ: Intelligence Quotient; OHSS: Ovarian Hyperstimulation Syndrome; FET: Frozen Embryo Transfer.

Although the majority of research findings on neurodevelopmental and mental health outcomes in ART-conceived individuals are reassuring, as evidenced by the studies listed in Table 1, certain specific neurodevelopmental and

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mental health conditions still require further investigation, as outlined in Table 2.

ART-conceived children generally exhibit language, motor, and adaptive behaviour skills comparable to those of naturally conceived children, with some studies noting slightly enhanced social development, particularly in male ART offspring [14]. No significant differences between ART-conceived and spontaneously conceived children have been observed in verbal skills, cognitive function, visual-motor ability, or attention during early school age [19]. Additionally, there are no disparities in neurodevelopment, growth, vision, or hearing between children conceived via ICSI and those conceived naturally [25]. Another study found no statistically significant differences in neurodevelopmental or physical health between children conceived via in-vitro procedure of assisted reproduction and natural conception at a mean age of 5.5 years, although limitations in the study's power and attrition may have masked subtle effects [24]. Furthermore, no heightened risk of neurocognitive development issues or ASD have been identified in children born after ART, particularly after adjusting for multiple births [22] and neurodevelopmental outcomes at age 2 are similar between ART-conceived children and those conceived naturally [28]. Additionally, mental health and social or cognitive developmental problems at ages 7–8 are generally comparable between ART and naturally conceived children, with some gender-specific differences noted [30]. Preterm infants born before 29 weeks of gestation and conceived via ART have been found to have lower odds of adverse neurodevelopmental outcomes, particularly in cognitive and language development, when assessed at 18 to 24 months of corrected age [18]. Moreover, ART-conceived children, such as term singletons, who may experience delayed growth and neurodevelopment in early infancy, typically catch up to their naturally conceived peers by 24 months of age [31]. Importantly, no increased risk of hospitalisation for cognitive and motor development issues has been identified in ART-conceived children after adjusting for shared genetic, environmental, and familial factors up to 11 years of age [17].

Studies indicate that there is no increased risk of neurodevelopmental disorders such as ASD, language delay, or global developmental delay in children conceived by ART, although an association between frozen embryo transfer (FET) and language delay has been noted in another study; however, further studies are required [20]. Another research study reported no significant difference in neurodevelopmental disorder risk between children born after frozen and fresh embryo transfer [34]. However, one study found an increased adjusted risk of learning and motor functioning disorders and conduct disorders in ART-conceived singletons compared with non-ART singletons, albeit with only small differences observed in neurodevelopment between the two groups [32]. A modest link was observed between parental subfecundity and neurodevelopmental delays in ART-conceived children [16], while another study showed a higher risk of delayed neurological development in ICSI-born infants than in naturally conceived children [39]. A review study highlighted the factors affecting neurodevelopmental outcomes in IVF-conceived twins, including foetal/intrauterine growth restriction, prematurity, and zygosity [38]. The study observed no documented impact of IVF itself on neurodevelopmental outcomes in IVF-conceived twins; however, the research highlighted the need for further research on this topic [38]. It is noteworthy that most literature shows no association between ART and poorer neurodevelopmental outcomes in ART-conceived offspring; however, research reporting such associations should be interpreted cautiously in the presence of confounders, as mentioned in a literature review by Perros et al. [1].

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The research shows no increased risk of hospitalisation for cerebral palsy (CP) in ART-conceived children after adjusting for shared genetic, environmental, and familial factors up to 11 years of age [17]. Nonetheless, an increased risk of CP has been observed in ART-conceived children, particularly those born preterm or as multiples, highlighting the heightened vulnerability of these groups [33], [40]. A review study relating to IVF-conceived twins observed a higher CP risk in term infants, those with growth restrictions, premature infants, and twins surviving co-twin intrauterine death, while emphasising the influence of certain confounding factors on neurodevelopmental outcomes in IVF twins [38]. The increased CP risk, compared with naturally conceived children, underscores the importance of considering the relevant confounders such as preterm birth and low birth weight in ART pregnancies [34].

Studies generally found no association between ART and an increased risk of ASD [21], [22], [26], or between IVF treatment and ASD risk compared with spontaneous conception [27]. Moreover, no increased risk of ASD diagnosis has been observed in ART-conceived singletons within their first three years of life [23], and there is no increased risk of hospitalisation for ASD in ART-conceived children up to 11 years of age after adjusting for certain factors [17]. However, some research findings indicate potential concerns. An association between FET and language delay has been reported, warranting further research [20]. Additionally, a small, elevated risk of autism has been observed in ICSI-conceived children, suggesting that severe male factor infertility and/or the use of ICSI might contribute to this risk; however, further research is warranted [37]. Another research study found ICSI children to be at higher risk of ASD than conventional IVF children [34]. Furthermore, toddlers conceived through ART may have a higher likelihood of failing ASD screenings, although these findings remain inconclusive [35]. The association between ART and ASD suggested in some studies highlights the need for further investigation [32], [41].

Children conceived via IVF/ICSI generally have lower rates of diagnosed ADHD compared with other conception groups. However, they exhibited slightly higher adjusted hazard ratios for ADHD [15]. Another study showed a higher tendency for increased risk of ADHD in ART-conceived singletons compared with non-ART singletons, although the differences in neurodevelopment between these two groups were small [32].

The research indicates that mental health or social and cognitive developmental problems are not different overall in ART-conceived children at 7 to 8 years compared with their naturally conceived peers. However, some gender-specific differences have been observed [30]. Furthermore, no increased risk of hospitalisation for cognitive issues has been reported in ART-conceived children after adjusting for certain shared factors [17]. Conversely, a higher risk of intellectual disability has been noted in ICSI-conceived children compared with those conceived via conventional IVF [34], and research suggests that IVF twins at age 4 may exhibit less favourable health and development, including lower IQ, body weight, and height, than IVF singletons of the same age. However, IVF was not considered a direct contributing factor [42]. Moreover, a review study on IVF-conceived twins linked certain confounding factors to differences in cognitive ability between twins and singletons [38]. Concerns have also been raised about reduced IQ in young children of ovarian hyperstimulation syndrome (OHSS) IVF women compared with non-OHSS IVF children, with prenatal estradiol exposure suggested as a possible underlying mechanism [43].

A Danish prospective nationwide cohort study did not find an overall increase in risk of adverse mental health outcomes in children with ART exposure during follow-up in childhood, adolescence or early adulthood; however, the study lacked statistical power to exclude the possibility of an effect of ART on specific mental health disorders [29]. Another research study reported no overall differences in mental health or social and cognitive developmental problems in ART children at 7 to 8 years compared with naturally conceived peers [30]. Nevertheless, another study showed slightly elevated risk of psychiatric diagnoses extending into young adulthood in ART-conceived children compared with a control group [36]. Additionally, research reported a higher risk of delayed psychological development in infants born through ICSI than in children conceived naturally [39]. A review study on IVF-conceived twins reported limited evidence for differences in behavioural and psychiatric disorders between twins and singletons, while highlighting the influence of certain confounding factors on neurodevelopmental outcomes in IVF-conceived twins, as well as the need for further research on the impact of IVF on these outcomes [38]. Another study suggested a small increase in the risk of mental retardation in ICSI-conceived offspring, where severe male factor infertility and the use of ICSI may be the contributory factors [37]. However, further research is needed to clarify these findings.

Impact of ART on Cardiometabolic Health in ART-Conceived Individuals:

This literature review included a total of 18 research studies on the impact of ART on cardiometabolic health in ART-conceived individuals, the findings of which are categorised into favourable and adverse in this population (Tables 3 and 4). These study results are further elaborated upon in the discussion section, which offers a more in-depth analysis of the findings.

Table 3. Favourable Research Findings on Cardiometabolic Health in ART-Conceived Individuals

SN	Author, Ref. & Year of Publication	Favourable Research Findings on Cardiometabolic Health in ART-Conceived Individuals
1	Elhakeem et al. [44] (2023)	Similar blood pressure, heart rate, triglycerides, and glucose measurements in ART-conceived offspring compared with naturally conceived offspring.
2	Penova-Veselinovic et al. [45] (2022)	No adverse effect of ART on most cardiometabolic parameters at adolescence.
3	Wijs et al.[46] (2022)	Similar or more favourable cardiometabolic and vascular health parameters in adolescents conceived through ART compared with their same-aged, non-ART peers.
4	Yeung et al.[47] (2022)	No increased cardiometabolic risk in ART-conceived children compared with those conceived without treatment at age 9.
5	Wei et al. [17] (2022)	No association of ART with hospitalisation for cardiovascular or metabolic disorders in children up to 11 years of age.
6	Magnus et al.[48] (2021)	No difference in height, weight, or BMI by age 17 between ART-conceived and naturally-conceived offspring.
7	Huang et al.[49] (2021)	No adverse early childhood cardiometabolic outcomes in ICSI-IVF offspring of subfertile couples despite effects on stature. Study results were found to be internally inconsistent.
8	Norrman et al.[50] (2021)	No difference in cardiovascular disease or type 2 diabetes risk between children born after ART and children born after spontaneous conception.

9	Juonala et al.[51] (2020)	No increased vulnerability to cardiovascular risk factors in ART-conceived individuals compared with those conceived without ART at age 22-35.
10	Halliday et al. [52] (2019)	No increased vascular or cardiometabolic risk or growth or respiratory problems in ART-conceived adults aged 22-35 compared with non-ART participants of the same age.

ART: Assisted Reproductive Technology; IVF: In Vitro Fertilisation; ICSI: Intracytoplasmic Sperm Injection; BMI: Body Mass Index.

Table 4. Adverse Research Findings on Cardiometabolic Health in ART-Conceived Individuals

SN	Author Ref. & Year of Publication	Adverse Research Findings on Cardiometabolic Health in ART-Conceived Individuals
1	Elhakeem et al. [44] (2023)	Higher total cholesterol, LDL cholesterol, and HDL cholesterol in ART-conceived offspring than in naturally conceived offspring. Lower blood pressure during childhood and subtle trajectories to nominally higher systolic blood pressure and triglycerides in young adulthood with ART warrant more extended follow-up studies.
2	Penova-Veselinovic et al. [45] (2022)	The observed increase in visceral adipose tissue in ART-conceived individuals warrants further investigation.
3	Zhang et al.[53] (2022)	Adverse cardiometabolic changes in offspring born after FET to overweight/obese mothers.
4	Zhu et al.[54] (2022)	Association of early pregnancy OHSS with elevated blood pressure in singletons aged 3-6 years conceived after IVF with or without ICSI.
5	Norrman et al.[50] (2021)	Significantly increased obesity risk in ART-conceived children.
6	Heber and Ptak[55] (2021)	Evidence of adverse metabolic alterations associated with ART at a young age that could lead to chronic adult-onset diseases like metabolic syndrome, type 2 diabetes, and cardiovascular disease later in life.
7	Norrman et al. [56] (2020)	Concern for the association of FET with increased risk of type 1 diabetes in singleton ART children.
8	Rumbold et al.[37] (2019)	Accelerated postnatal growth in ICSI children and risk of increased adiposity, particularly in girls.
10	Esteves et al.[39] (2018)	Greater risk of impaired cardiometabolic profile in infants born through ICSI than in those conceived naturally.
11	Meister et al.[57] (2018)	Association of ART with premature vascular aging in apparently healthy adolescents and young adults.
12	Catford et al.[25] (2018)	Greater susceptibility to adiposity and early insulin resistance in children conceived through ICSI than in spontaneously conceived peers; however, some inconsistent results warrant further research.
13	Belva et al.[58] (2018)	Lower mean HDL cholesterol in young adult men conceived by ICSI compared with the spontaneously conceived control group.

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14	Hann et al.[59] (2018)	ART babies from fresh embryo transfer grow more slowly in utero and during the first few weeks of life but catch up by school age compared with naturally conceived and FET babies, potentially raising their risk for cardiometabolic diseases in later life.
15	Guo et al.[60] (2017)	Higher fasting insulin levels, higher blood pressure (statistically significant), and lower LDL cholesterol in IVF-ICSI offspring than in offspring conceived naturally; elevated risk of cardiovascular disease among IVF-ICSI offspring.
16	Vrooman and Bartolomei [61] (2017)	Epidemiological evidence of differences in blood pressure, body composition, and glucose homeostasis in ART-conceived children.
17	Kuiper et al.[42] (2017)	Less favourable health and development (lower total IQ, body weight, and height) in 4-year-old IVF twins than 4-year-old IVF singletons, not altered by IVF per se.

LDL Cholesterol: Low-Density Lipoprotein Cholesterol; HDL Cholesterol: High-Density Lipoprotein Cholesterol; ART: Assisted Reproductive Technology; IVF: In Vitro Fertilisation; ICSI Intracytoplasmic Sperm Injection; FET: Frozen Embryo Transfer; OHSS: Ovarian Hyperstimulation Syndrome; IQ: Intelligence Quotient.

Research highlights the complexities relating to cardiometabolic health in individuals conceived through ART. While several studies [17], [45], [46], [47], [48], [49], [50], [51], [52] suggest an overall reassuring outlook, as shown in Table 3, specific concerns persist, as outlined in Table 4. The research findings regarding the impact of ART on cardiometabolic health are discussed below.

Several studies report generally reassuring cardiometabolic health in ART-conceived individuals. For instance, one study found no increased vascular or cardiometabolic risk in ART-conceived adults aged 22-35 compared with non-ART participants of the same age [52]. Another study found no association between ART and hospitalisation for cardiovascular or metabolic disorders in children up to 11 years of age [17]. While many studies report reassuring overall cardiometabolic health [17], [45], [46], [47],[49],[52],some research on ART-conceived individuals has raised concerns about lipid profiles [44], [58]. For example, research indicated that while blood pressure, heart rate, and triglycerides in ART-conceived offspring were similar to those of naturally conceived offspring, ART-conceived individuals exhibited higher levels of total, LDL, and HDL cholesterol, with lower blood pressure during childhood and subtle trajectories to nominally higher systolic blood pressure and triglycerides in young adulthood, suggesting cardiometabolic alterations [44]. Another study reported that young adult men conceived via ICSI had lower mean HDL cholesterol levels compared with a spontaneously conceived control group [58]. Furthermore, research found elevated blood pressure and lower LDL cholesterol in IVF-ICSI offspring than in naturally conceived offspring [60].

On the other hand, some studies have raised concerns about potential cardiometabolic alterations in ART-conceived individuals. For instance, infants born via ICSI were found to have a more impaired cardiometabolic profile compared with naturally conceived children [39]. The adverse metabolic alterations associated with ART at a young age could lead to chronic adult-onset diseases like metabolic syndrome and cardiovascular disease later in life [55]. Concerns have been raised about the potential risk of developing cardiometabolic diseases in later life for individuals born through fresh embryo transfer [59], while other research showed an association between FET and adverse cardiometabolic changes in offspring born to over-

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weight/obese mothers [53]. Another study suggested that early pregnancy OHSS might independently influence offspring's blood pressure and potentially impact cardiovascular function in ART-conceived singletons aged 3 to 6 years. However, no significant adverse effects on anthropometrics and metabolic function were observed [54].

Several studies provide a more positive outlook on the cardiovascular health of ART-conceived individuals [17], [46], [50], [51], [52], [55]. One study found no association between ART and hospitalisation for cardiovascular or metabolic disorders in children up to 11 years of age [17]. Another observed that, while blood pressure, heart rate, and triglycerides in ART-conceived offspring were similar to those of naturally conceived offspring, ART-conceived individuals exhibited lower blood pressure during childhood and subtle trajectories to nominally higher systolic blood pressure and triglycerides in young adulthood [44]. Some research studies offer reassurance by indicating no elevated vascular risk [52] or cardiovascular risk [51] in ART-conceived individuals aged 22 to 35, compared with those conceived without ART. However, other studies have identified potential risks. For instance, one study highlighted cardiovascular health-related issues in ART children, including increased blood pressure in ART singletons that persists into adolescence [22]. Another study found statistically significant higher blood pressure in IVF-ICSI offspring than in naturally conceived offspring, suggesting an elevated cardiovascular risk [60]. There is epidemiological evidence pointing to differences in blood pressure, body composition, and glucose homeostasis in children conceived through ART [61]. Additionally, research suggests an association between early pregnancy OHSS and elevated blood pressure in IVF-conceived singletons aged 3 to 6 years (with or without ICSI), suggesting that opting for frozen-thawed embryo transfer in high-risk OHSS populations may reduce this risk [54].

The growth and obesity-related research in ART-conceived individuals show a mix of reassuring and concerning findings. One study found no significant differences in height, weight, or BMI by age 17 between ART-conceived and naturally conceived individuals, indicating similar growth patterns [48]. This is consistent with findings from another study that reported comparable BMI between IVF-ICSI offspring and naturally conceived offspring [60]. Furthermore, a study found no adverse early child cardiometabolic outcomes in ICSI-IVF offspring despite effects on stature [49]. Conversely, other studies have highlighted concerns. For instance, accelerated postnatal growth and an increased risk of adiposity were noted particularly in ICSI-conceived girls [37]. Research also found ICSI-conceived children to be more susceptible to adiposity than spontaneously conceived peers; however, some inconsistent results warranted further research [25]. Another study reported increased visceral adipose tissue in ART-conceived adolescents [45], while yet another found a higher risk of obesity in ART-conceived children [50]. Moreover, one study reported less favourable health and development, including lower IQ, body weight, and height, in 4-year-old IVF twins than in 4-year-old IVF singletons, although IVF was not considered a contributing factor [42].

Some concerns have also been identified with regard to long-term risks. One study pointed to premature vascular aging as a potential risk in ART-conceived individuals, particularly in otherwise healthy adolescents and young adults [57]. A review study reported evidence of ART-associated adverse metabolic alterations at a young age, potentially increasing the risk of chronic adult-onset diseases such as metabolic syndrome, type 2 diabetes, and cardiovascular disease later in life [55]. Moreover, concerns have been raised about the potential risk of cardiometabolic diseases later in life for individuals born via fresh embryo transfer [59].

The risk of diabetes and glucose regulation problems in ART-conceived individuals has been a focus of various studies, with mixed findings. On the positive side, one study observed that glucose measures in ART-conceived offspring were similar to those in naturally conceived offspring [44]. Another study found no increased risk of type 2 diabetes between children born after ART and those born through spontaneous conception [50]. Conversely, other studies suggest potential risks. Concerns have been raised about a potential association between FET-conceived singletons and an elevated risk of type 1 diabetes [56]. Moreover, epidemiological evidence indicated that ART-conceived children exhibit cardiometabolic alterations, including differences in glucose homeostasis [61]. Additional research found higher fasting insulin levels in IVF-ICSI offspring than in naturally conceived offspring [60], while a further study reported increased susceptibility to early insulin resistance in children conceived through ICSI compared with spontaneously conceived peers, although some inconsistent results warrant further investigation [25]. There is also evidence from a review study that ART may be associated with adverse metabolic alterations at a young age, potentially leading to chronic adult-onset diseases such as metabolic syndrome, type 2 diabetes, and cardiovascular disease later in life [55]. Lastly, research has pointed to a higher risk of type 1 diabetes in children conceived through cryopreserved embryos [22].

IV. DISCUSSION

While most research on ART-conceived children reports reassuring neurodevelopmental and mental health, comparable to naturally conceived peers, particular concerns persist. ART children generally exhibit similar language, motor, and adaptive behaviour skills, with no significant differences in verbal, cognitive, or visual-motor abilities. However, specific subgroups, such as those conceived via ICSI, may have an elevated risk of intellectual disability and neurodevelopmental disorders, including autism spectrum disorder. Additionally, an association between FET and language delay has been observed, warranting further research. Children born prematurely or as multiples after ART are also at a higher risk for conditions like cerebral palsy. Although overall mental health in ART-conceived children is comparable to their peers, an increase in the risk of psychological and neurological development delays has been noted, particularly in ICSI cases. Continued research is crucial to fully understand the long-term neurodevelopmental outcomes in ART-conceived children, especially as reproductive technologies evolve.

Current research on cardiometabolic health in ART-conceived individuals presents a complex and evolving landscape. While many ART off spring exhibit a generally favourable impact of ART on cardiometabolic health, emerging concerns regarding elevated blood pressure, altered lipid profiles, obesity, and metabolic changes suggest potential long-term health risks. Evidence highlights the possibility of premature vascular aging and greater susceptibility to chronic conditions, including metabolic syndrome and type 2 diabetes, in ART-conceived individuals. Specific subgroups, such as those conceived via ICSI, appear to be at a heightened risk, with increased susceptibility to adiposity and insulin resistance, warranting further investigation. Additionally, a higher risk of type 1 diabetes has been reported in individuals conceived through FET. Continued monitoring and research are essential to understand and mitigate these potential long-term cardiometabolic risks in ART-conceived individuals.

An essential caveat is the variability in methodologies, sample sizes, and follow-up periods of the studies reviewed. This diversity can lead to inconsistent findings and make it challenging to

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draw definitive conclusions. Inherent biases in the research, including selection and information bias, are possible. This review emphasises observed associations rather than definitive causality. The intricate interplay of genetic, environmental, and epigenetic factors in ART-related health outcomes underscores the complexity of establishing clear causal relationships.

The findings imply that while ART is generally safe and effective, specific subgroups of ART-conceived individuals may be at an increased risk for specific neurodevelopmental and cardiometabolic challenges. Children conceived via ICSI are at higher risk of intellectual disability, neurodevelopmental disorders such as autism spectrum disorder, and psychological and neurological development delays, as well as metabolic concerns such as increased adiposity and insulin resistance. This highlights the importance of implementing long-term neurodevelopmental and metabolic monitoring for ICSI-conceived children to ensure optimal long-term health outcomes. Moreover, children conceived via FET have an elevated risk for language delay and type 1 diabetes, warranting further research in this area. To mitigate these risks, healthcare providers should prioritise early screening for language development and type 1 diabetes in FET-conceived children, ensuring timely and targeted interventions. The increased risk of cerebral palsy in children born as multiples or prematurely following ART requires careful consideration in both the medical management of ART and neonatal care. Additionally, cardiometabolic concerns in ART-conceived individuals, such as increased risks of high blood pressure, altered lipid profiles, obesity, insulin resistance, premature vascular aging, and adverse metabolic changes, underscore the importance of continuous monitoring and early interventions. These measures are essential to mitigate the potential development of chronic conditions later in life, including metabolic syndrome, type 2 diabetes, and cardiovascular disease. Robust research, including long-term follow-up studies on ART-conceived individuals, is essential to accurately determine the long-term health outcomes in this population.

V. CONCLUSION

The relationship between ART and specific long-term health impacts in ART-conceived individuals is complex, highlighting the need for ongoing research and careful consideration. While most neurodevelopmental and mental health outcomes are generally comparable to naturally conceived peers, specific subgroups face elevated risks. Children conceived via ICSI may have a higher risk of neurodevelopmental disorders, including autism spectrum disorder, intellectual disability, and psychological and neurological development delays. Additionally, frozen embryo transfer has been associated with an increased likelihood of language delay, and children born as multiples or prematurely after ART have a heightened risk of conditions like cerebral palsy. Further research is essential to clarify these risks and improve long-term outcomes.

Regarding cardiometabolic health, although many ART-conceived individuals demonstrate favourable profiles, emerging concerns include increased risks of high blood pressure, altered lipid levels, obesity, insulin resistance, premature vascular aging, and adverse metabolic changes. ICSI-conceived individuals may be at higher risk for adiposity and early insulin resistance, while those conceived via frozen embryo transfer have shown associations with type 1 diabetes. These findings underscore the importance of continued monitoring, research, and targeted interventions to mitigate potential long-term risks as reproductive technologies evolve.

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