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Review

A Scoping Review: Risk of Autism in Children Born from Assisted Reproductive Technology

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Abstract: Background/Objectives: As the incidence of autism spectrum disorder (ASD) and use of assisted reproductive technologies (ART) continue to rise in tandem, their relationship to one another, as well as the general risks of ART, are increasingly being explored. The purpose of this review is to summarize the literature on ASD risk, as well as the risks for other neurological and neurodevelopmental disorders, in children born following the implementation of ART. **Methods**: Here we review studies published between 2000−2023 that elucidate relationships between ASD and some of the most common forms of ART, including in vitro fertilization (IVF) and intracytoplasmic sperm injection (ICSI), using fresh vs. frozen embryo transfer. Articles were identified by searching Google Scholar and PubMed databases. **Results**: Though some studies report adverse neurodevelopmental outcomes in ART-conceived children, such as ASD, attention-deficit/hyperactivity disorder (ADHD), and cerebral palsy, a majority of studies do not show a significant association between ART and neurodevelopmental disorders. Additionally, many confounding factors like multiple and preterm births, underlying infertility, and advanced parental age have been discussed, highlighting the need for studies that effectively control for these confounders. Potential mechanisms implicated in the pathogenesis of ASD, including epigenetic mechanisms of gene expression, that may be related to ART procedures, are also discussed. **Conclusion**: ART may pose a low additional risk to development of ASD, but confounding factors likely account for most of this risk. Several steps in the process of ART may cause epigenetic changes that are implicated in the development of ASD.

Keywords: assisted reproductive technology; autism spectrum disorder; infertility; in vitro fertilization; intracytoplasmic sperm injection; frozen embryo transfer; neurodevelopmental disorders

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1. Introduction

Infertility is a disease of the male or female reproductive system, defined as the failure to achieve pregnancy after 12 months or more of regular, unprotected sexual intercourse [1]. According to the European Society of Human Reproduction and Embryology (ESHRE) [2], 1 in 6 couples worldwide experience infertility at least once during their reproductive lifetime. In the United States, the prevalence of impaired fecundity—defined as difficulties in getting pregnant and/or carrying a baby to term—for all women, regardless of marital status, was estimated at 13.4% between 2015–2019 [3], an increase from 12.1% between 2011–2015 [4].

As a solution to infertility, assisted reproductive technologies (ART) have been developed and are increasingly being used by couples seeking to achieve pregnancy. Since the first successful birth via in vitro fertilization (IVF) in the United Kingdom in 1978 [5], it is estimated that over 10 million children have been conceived globally using ART, with the highest prevalence in Europe at a reported 1,007,598 treatment cycles initiated compared to the 306,197 cycles initiated in the United States in 2018 [2].

ART encompasses several types of procedures used to treat infertility and achieve pregnancy. Based on the 1992 Fertility Clinic Success Rate and Certification Act, the Centers for Disease Control and Prevention (CDC) defines ART as all fertility treatments in which either eggs or embryos are handled, excluding treatments like artificial insemination in which only sperm are handled [6]. Some examples of ART include IVF with fresh or frozen embryo transfer, intracytoplasmic sperm injection (ICSI), gamete intrafallopian transfer (GIFT), and zygote intrafallopian transfer (ZIFT), among others.

Autism spectrum disorder (ASD) is a neurodevelopmental disorder characterized by social and communication impairments and restricted or repetitive behaviors [7]. According to a recent review of the global prevalence of autism, approximately 1 in 100 children are diagnosed with ASD worldwide [8]. In the United States, the prevalence of ASD among 8-year-olds has steadily increased, reaching 1 in 36 children in 2020 [9]. With the rise in ASD diagnoses, the breadth of research investigating genetic and environmental risk factors has continued to grow as well [10]. Several environmental risk factors have been described, including advanced parental age, maternal nutrition, maternal infections and diseases, environmental toxins, and medications [11]. Of these, ART has also been identified as a potential risk factor for ASD, and many of the associated risks, such as hormonal disturbances, advanced maternal age, preterm birth, and low birth weight, are implicated in both [11]. Infertility itself is also considered to be an environmental risk factor for ASD [12] and has been associated with neurodevelopmental disorders [13], particularly in the context of vitamin D deficiency [14]. As vitamin D is important in the stability of cell signaling systems, disruptions in these signaling pathways during development can lead to infertility and the onset of neurodevelopmental diseases. A recent article by Velez et al. [15] reported a slightly higher risk of ASD in children born to individuals with infertility who did not receive fertility treatment, known as subfertility. Another study found a higher risk of ADHD in children born to mothers with subfertility, which was not amplified after using fertility treatment [16]. It has been shown that women with subfertility but no ART history are more likely to have adverse perinatal outcomes [17–20] which are associated with a higher likelihood of ASD [21]. Thus, although the increases in both ART use and incidence of ASD call into question whether the two might be related, it is crucial to consider infertility itself as a significant risk factor.

Given the impact ART has made on infertility and its increasing global use, it is important to examine the potential short- and long-term effects in offspring, especially regarding neurodevelopmental disorders like ASD. While associations between ART and ASD have been debated in the literature, the results remain inconclusive. In this review, we will summarize the findings in the literature and explore the relationship between ASD and ART, both in general and with respect to specific ART procedures.

2. Materials and Methods

2.1. Literature Search and Identification

We conducted a thorough literature search using the databases Google Scholar and PubMed. In 2021, Google Scholar database was estimated to contain approximately 389 million documents, making it the world's largest academic search engine as of January 2018 [22]. The PubMed database comprises more than 37 million citations for biomedical literature from MEDLINE, life science journals, and online books. The search terms inputted into the databases included keywords or terms that we considered to be relevant to our review. Examples included "Assisted reproductive technology and ASD" and "ART and autism." We then conducted another search using the same method to identify articles related to specific types of ART and ASD. The search terms for this search included "ICSI and ASD" and "IVF and ASD", for example. Research articles did not have to be mutually exclusive to one specific form of ART to be included in this review paper. The number of returns from the keywords into the search engine was logged to determine if similar research articles were found with the associated keywords. Articles were selected based on their title that were about both ART and ASD or other neurodevelopmental outcomes,

as well as ART subcategories: IVF, ICSI, and fresh vs. frozen embryo transfer. If we could not determine whether the article was appropriate to include in this review, we also read the abstract. For each search, once we encountered between five and ten articles in a row that were not relevant to our topic, that search was terminated. Additional articles were identified using the bibliographies of the articles retrieved from the initial database search. Only peer-reviewed research articles were included, not abstracts, conference proceedings, or theses. Publication dates for the included articles were kept between 2000 and 2023.

2.2. Inclusion and Exclusion Criteria

Research articles included in this review focused on the procedures of either IVF, ICSI, and/or fresh/frozen embryo (cryopreservation) techniques. Other studies included in this review focused on ASD and the neurodevelopment of embryos procured from ART. Research articles that were original research, meta-analysis and review papers were included.

GIFT and ZIFT techniques involve laparoscopic egg retrieval and intra-tubal transfer of either male and female gametes (GIFT) or zygotes (ZIFT) [5]. However, unlike ZIFT and IVF, GIFT involves fertilization in vivo which precludes confirmation of fertilization and assessment of embryo quality [23]. Both GIFT and ZIFT procedures require general anesthesia with intubation, and thus are considered more invasive than IVF, ICSI, and the possible cryopreservation of male and female gametes and embryos which can be done under local anesthesia or deep sedation [5]. Additionally, because transfer is made into the fallopian tube instead of the uterus, GIFT and ZIFT are limited to patients with at least one healthy fallopian tube. Other disadvantages of GIFT/ZIFT include cost, increased risk for ectopic pregnancy [24], and the addition of laparoscopy with no significant advantage in pregnancy rates compared to IVF and embryo transfer [25,26]. For these reasons, GIFT and ZIFT are rarely done today. Therefore, we did not examine their association with ASD in this review.

3. Results

3.1. Assisted Reproductive Technology

The consequences of ART are difficult to ascertain due to several challenges, such as inadequate sample sizes and limited studies assessing long-term effects, as the oldest individuals conceived via ART are only now reaching their early 40s. In particular, the lack of large-scale studies has made it difficult to investigate the role of ART in ASD apart from other neurological pathologies [27] (Table 1). Additionally, several confounding factors have been identified, which complicate the matter further. Because of these obstacles, there is a lack of solid evidence to support a direct correlation between ART and specific outcomes, like ASD, in offspring. However, the studies that have been conducted are generally reassuring and suggest that ART is a safe option for couples seeking infertility treatment.

Table 1. Effects of ART in general on neurodevelopmental outcomes in children.

Study Design	Sample Size	Country	Specific Neurodevelopmental Outcome(s)	Results	Source
Meta-analysis	15 studies (7 cohort, 8 case-control)	USA Europe Asia	ASD	Positive correlation, not confirmed in singletons	Andreadou 2021 [28]
Meta-analysis	11 studies (3 cohort, 8 case-control)	USA Europe Asia	ASD	1.35 times greater risk compared to spontaneous conception	Liu 2017 [29]

Table 1. *Cont.*

Study Design	Sample Size	Country	Specific Neurodevelopmental Outcome(s)	Results	Source
Meta-analysis	10 studies (8 cohort, 2 case-control)	USA Denmark Australia Finland Sweden	ASD, CP, intellectual disability, behavioral problems	No significant increased risk of ASD, intellectual disability, or behavioral problems Increased risk of CP	Djuwantono 2020 [30]
Literature review	24 studies (10 review/meta-analysis, 12 cohort/retrospective cohort, 2 case-control)	Denmark Finland Sweden USA Europe Asia Australia Iran The Netherlands Taiwan	Neurodevelopmental pathologies (including ASD), infantile CP, poorer school cognitive performance	Not correlated with neurodevelopmental pathologies 2 studies showed positive correlation with CP Not correlated with worsening cognitive performance, improved school cognitive performance seen in 2 studies	Gullo 2022 [31]
Literature review	21 studies	Denmark Sweden Finland USA	ASD, CP, intellectual disability, epilepsy, ADHD	Increased risk of CP and epilepsy No increased risk of intellectual disability Data on ASD and ADHD are uncertain	Källén 2014 [32]
Literature review	Not specified	USA India Europe Asia Finland Denmark Iran	ASD	No significant increased risk but results inconclusive	Saxena 2021 [33]
Literature review	20 studies	The Netherlands Denmark Australia Sweden USA Australia	CP, cognitive development, ADHD, ASD	When restricted to singletons, neurodevelopmental outcomes are similar between ART-conceived and SC children	Bergh 2020 [34]
Literature review	32 studies	Israel United Kingdom Belgium Sweden USA The Netherlands Denmark	Neurocognitive and motor development	No differences between ART-conceived and SC children	Abdel-Mannan 2014 [35]

Table 1. *Cont.*

Study Design	Sample Size	Country	Specific Neurodevelopmental Outcome(s)	Results	Source
Long-term follow up of a prospective cohort	358 mothers of ART-conceived children 401 mothers of SC children	Israel	Developmental coordination disorder, short sensory profile, ASD, ADHD	No significant differences between ART-conceived and SC groups regarding developmental coordination disorders or short sensory profile Results for ASD and ADHD are inconclusive	Fahri 2021 [36]
Literature review	50 studies	Not specified	Cognitive, motor, and language development, behavior problems	Majority of studies showed no increased risk of cognitive, motor, or language development disorders Lower IQ scores, worse visual-motor ability, and delayed receptive language was seen in ART-conceived group Higher prevalence of behavior problems in ART-conceived group	Zhan 2013 [37]
Systematic review	7 studies (2 cohort, 5 case-control)	Denmark Israel Japan Finland	ASD	4 studies (best quality scores) showed no correlation 2 studies (lowest quality scores) showed increased risk 1 study showed protective role of ART	Conti 2013 [38]
Literature review	35 studies	Australia Canada Denmark UK USA Taiwan Israel The Netherlands Iran Finland Belgium Sweden Japan Germany	ASD	No association	Perros 2022 [39]
Population-based	513 cases 388 controls	USA	ASD	No significant increased risk	Lyall 2013 [40]

Table 1. *Cont.*

Study Design	Sample Size	Country	Specific Neurodevelopmental Outcome(s)	Results	Source
Cohort	ART dataset: 248 cases 496 controls ASD dataset: 83 cases 332 controls	Taiwan	ASD	No association	Lung 2018 [41]
Case-control	100 cases 200 controls	Iran	Neurodevelopmental outcomes	No association	Jenabi 2020 [42]
Case-control	2760 children	USA	ASD	No significant differences in copy number variations or autism-associated gene-disrupting events found	Ackerman 2014 [43]
Population-based case-control	1538 mother–child pairs	USA	ASD	No association	Schieve 2017 [44]
Longitudinal cohort	460,117 singletons: 10,147 ART 8072 subfertile 441,898 fertile	USA	ASD	No increased risk	Diop 2019 [45]
Meta-analysis	18 studies (7 cohort, 11 case-control)	Poland USA Iran Denmark Sweden Turkey Finland Japan Israel Taiwan	ASD	No association	Jenabi 2022 [46]
Survey/questionnaire	Biological parents of 121 ASD children and 100 healthy children	Poland	ASD	No statistically significant influence	Magdalena 2020 [47]
Mathematical assessment model	75 scenarios of RFP, cRFP, and RR	USA	ASD	No substantive contribution to the increase in ASD prevalence	Schieve 2011 [48]
Prospective cohort	4824 mothers and 5841 children: 1830 conceived via infertility treatment	USA	Early childhood developmental domains (fine motor, gross motor, communication, personal-social functioning, and problem-solving ability)	Children's development through age 3 years was similar irrespective of infertility treatment or type after accounting for plurality	Yeung 2016 [49]

Table 1. *Cont.*

Study Design	Sample Size	Country	Specific Neurodevelopmental Outcome(s)	Results	Source
Nested case-control	507 cases 2529 controls	USA	ASD	No significant association with self-reported fertility therapies or history of infertility Significant association with AI among older women	Lyall 2012 [50]
Population-based cohort	Initial sample: 30,483 children (530 ART-conceived) Sample accounting for SES: 17,075 children (492 ART-conceived)	USA	ASD diagnosis age and symptom severity	No significant differences between ART-conceived and SC children in diagnosis age or symptom severity after adjusting for SES	Schieve 2015 [51]
Prospective cohort	15,218 children	UK	Cognitive development	Improved cognitive functioning	Barbuscia 2017 [52]
Population-based case-control	461 cases 461 controls	Denmark	ASD	Decreased risk	Maimburg 2007 [53]
Population-based cross-sectional survey	42,551 children	Vietnam	ASD	Increased risk	Vui 2023 [54]
Observational cohort	48,865 children	USA	ASD	2x increased risk	Fountian 2015 [55]
Population-based	5,076,444 children	Denmark Finland Norway Sweden	Learning and motor functioning disorders, ASD, ADHD	Small increased risk	Rönö 2022 [56]

Abbreviations: ASD, autism spectrum disorder; CP, cerebral palsy; ADHD, attention-deficit/hyperactivity disorder; ART, assisted reproductive technologies; AI, artificial insemination; RFP, risk factor prevalence; RR, relative risk; cRFP, change in RFP; SC, spontaneously conceived; SES, socioeconomic status.

Several meta-analyses have examined the relationship between ART and autism. A recent meta-analysis of 15 studies by Andreadou et al. [28] demonstrated a positive correlation between ART and ASD in offspring, though this was not seen in singleton pregnancies. These results suggest that multiple pregnancies may be an independent risk factor for ASD. The author's results also highlight the need to examine which variables play a primary vs. secondary role in the development of ASD in offspring. Another meta-analysis including 11 studies showed similar results, reporting that children born via ART are 1.35 times more likely to develop ASD than those conceived spontaneously, particularly in European and Asian populations [29]. While Djuwantono et al.'s [30] meta-analysis found that ART in general did not increase the risk of ASD, intellectual disability, or behavioral problems, they did report that this differed among different types of ART, and identified an increased risk of cerebral palsy in offspring with ART in general. However, the authors note the presence of confounding variables, such as preterm birth and low birth weight, which are known risk factors for cerebral palsy.

Several reviews have examined the neurological impact of ART on children, many of which include studies investigating ASD. In one such review, the majority of studies

did not identify a relationship between ART and autism, though two studies showed mixed results [31]. The authors also expressed concern about the increased risk of cerebral palsy, although the results were inconclusive. Kallen et al.'s [32] review similarly reported an increased risk of cerebral palsy and epilepsy with ART use, though no increased risk of intellectual disability was observed, and the data on ASD and ADHD risks remained unclear. A recent review by Saxena et al. [33] also identified variable results in the literature, deeming the association between ART and ASD to be inconclusive. Similarly to Andreadou et al. [28], a literature review by Bergh et al. [34] did not find a significant difference in neurodevelopmental outcomes, including cognitive development, ADHD, and ASD, between ART-conceived and spontaneously conceived children when restricted to singletons. The authors highlight the need for further large-scale studies, including more recent cohorts of ART children, to determine the true impact of ART on cerebral palsy risk. Regarding neurocognitive, motor, and language development, a majority of studies reported no increased risk with ART [35–37], although lower IQ scores, worse visual–motor ability, and delayed receptive language, in addition to a higher prevalence of behavioral problems, were observed in ART-conceived children [37]. Given these conflicting results, the associations between ART and neurodevelopmental problems in children remain largely undetermined.

Many studies show no evidence of a significant association between ART and ASD [38–48,57], and neurodevelopmental outcomes in general are reassuring [39,58,59], particularly after controlling for multiple births and preterm delivery [49,60], which are independently associated with neurodevelopmental delays and cerebral palsy [58]. A nested case-control study within the Nurses' Health Study II (n = 116,430) showed no associated risk of having a child with ASD with self-reported fertility therapies or history of infertility [50]. However, a subgroup analysis of women aged 35 and older in the same study revealed a significant association between ASD risk and artificial insemination, as well as the use of ovulation-inducing drugs. After controlling for potential covariates, however, only the association with artificial insemination remained significant. A population-based cohort study by Schieve et al. [51] reported no significant differences in ASD diagnosis age or symptom severity between ART-conceived and spontaneously conceived children after adjusting for socioeconomic status. Lastly, in a large, population-based case-control study by Lyall et al. [40], there was no evidence of strong increases in risk of ASD with ART, but they were not able to rule out subtler effects.

Interestingly, two studies found improved cognitive functioning in children born via ART, suggesting that factors other than mode of conception, like the educational level of the parents, have a greater contribution [52,61]. Another study by Maimburg et al. [53] reported a potential protective role of ART in children, indicating that certain advantages of ART, like more frequent contact with the healthcare system and good health behavior, especially during early pregnancy, lead to better health outcomes [38].

Conversely, some studies have found a relationship between ART and ASD. In Vietnam, a population-based cross-sectional survey given to parents of 42,551 children aged 18–30 months showed that the use of ART resulted in a higher risk of ASD amongst those children [54]. In an observational cohort study of 48,865 ART offspring born in California from 1997–2007, Fountain et al. [55] discovered that children born from ART were twice as likely as non-ART children to be diagnosed with ASD. However, these results were primarily explained by multiple births and adverse prenatal and perinatal outcomes. A study by Robinson et al. [62] used a screening tool for ASD, the Modified Checklist for Autism in Toddlers (M-CHAT), to assess the impact of ART (IVF with or without ICSI) and non-ART (ovulation induction with or without intrauterine insemination) fertility treatments. They found that infertility treatment in general was associated with M-CHAT failure at 18, 24, and 18 or 24 months. Of the infertility treatments assessed, both non-ART and ART treatments had positive associations with M-CHAT failure, though there were inconsistent associations with ICSI. It was also found that ART children had a higher risk of learning and motor functioning disorders as well ASD and ADHD compared to non-ART

children, though the differences between the two groups were small [56]. Comparing different types of ART, the authors found no increased risk of neurological disorders, including ASD, with IVF vs. ICSI or after fresh vs. frozen embryo transfer.

Although most studies are reassuring, the mixed results suggest that more research is needed. It is also important to consider the different types of ART used, and whether any of the individual techniques pose a neurodevelopmental risk to offspring. Here, we further explore the current literature surrounding the specific ART that are currently in common use: IVF, ICSI, and frozen vs. fresh embryo transfer; and their potential association with neurodevelopmental disorders like ASD.

3.2. In Vitro Fertilization

IVF is the treatment that leads to the highest pregnancy rate per cycle regardless of the cause of infertility [63]. Indications for IVF include acquired or congenital tubal disease, moderate male infertility when previous inseminations have failed, grade III or IV endometriosis, cryopreserved semen, and others [5]. The IVF cycle consists of ovarian stimulation, egg retrieval, in vitro fertilization, and embryo transfer into the uterus [5]. Compared to spontaneous conception, IVF is associated with more complications during pregnancy and delivery, and in infants [64]. IVF is also associated with an increased risk of low birth weight, preterm birth [65–67], perinatal mortality, neonatal intensive care admission [68,69], congenital defects [70–72], and increased chances of multiple gestations due to multiple embryo transfers during the procedure [5,73–75]. Although the rates of ART-conceived multiple pregnancies [76], as well as preterm and low birthweight deliveries [77], continue to decrease over time, the percentages remain higher than among infants conceived spontaneously [5,78].

Similar to ART as a whole, short-term neurodevelopmental outcomes in IVF-conceived children are generally reassuring [45,58,79,80] (Table 2), though a comparative analysis by Cheung et al. [81] reported impaired developmental characteristics in IVF-conceived children compared to those conceived via ICSI. There has been increasing investigation into the association between IVF and autism. Studies that have found a connection to ASD, however, can often be explained by confounding factors such as adverse prenatal and perinatal outcomes and multiple births [55,82]. Although Diop et al. [45] found no direct correlation between ASD and ART, they did confirm associations between preterm birth and ASD and between ART and preterm birth, suggesting ART may not be an independent risk factor for the development of ASD.

Table 2. Effects of IVF on neurodevelopmental outcomes in children.

Study Design	Sample Size	Country	Specific Neurodevelopmental Outcome (s)	Results	Source
Population-based, prospective cohort	Cases: 103 children with ASD conceived by IVF; 180 children with mental retardation conceived by IVF	Sweden	ASD, mental retardation	Not correlated with ASD Small but statistically significant increased risk of mental retardation	Sandin 2013 [57]
Systematic Review	87 studies	Sweden Belgium Denmark Australia United Kingdom The Netherlands USA Germany Greece Canada	ASD, ADHD, CP, developmental delay, poor cognitive function and school performance, depression and anxiety	Evidence is reassuring with regard to longer-term mental health outcomes Potential increased risk of CP and slight developmental delay	Hart 2013 [58]

Table 2. *Cont.*

Study Design	Sample Size	Country	Specific Neurodevelopmental Outcome (s)	Results	Source
Longitudinal cohort	4834 children	USA	ASD	No increased risk	Diop 2019 [45]
Case-control	4164 cases 16,582 controls	Finland	ASD	No increased risk	Lehti 2013 [79]
Population-based cohort	14,991 IVF children	Denmark	ASD	Increased risk in IVF subgroup	Hvidtjørn 2011 [82]
Population-based cohort	108,548 children 83,452 parents	Israel	ASD	No statistically significant association	Davidovitch 2018 [12]
Prospective register-based cohort	SC: 555,828 IVF/ICSI: 14,991 OI/IUI: 18,148	Denmark	Mental disorders	No increased risk with IVF or ICSI Small increased incidence with OI and IUI	Bay 2013 [83]
Clinical case and literature review	Not specified	Morocco Sweden Nordic countries Israel	ASD, Tourette syndrome	Small but statistically significant increased risk	Berrada 2022 [84]
Population-based cohort	79 IVF-conceived children 79 SC controls	Saudi Arabia	School performance and long-term outcomes (ASD, ADHD, visual or hearing impairment)	No significant difference between IVF-conceived and SC children	Al-Hathlol 2020 [80]
Comparative analysis	IVF: 451 questionnaires ICSI: 1914 questionnaires	USA	Development and behavior	IVF conceived children had impaired developmental characteristics compared to ICSI-conceived cohort	Cheung 2021 [81]

Abbreviations: IVF, in vitro fertilization; ICSI, intracytoplasmic sperm injection; ASD, autism spectrum disorder; CP, cerebral palsy; ADHD, attention-deficit/hyperactivity disorder; OI, ovulation induction; IUI, intrauterine insemination; SC, spontaneously conceived.

Additionally, a cohort study by Davidovitch et al. [12] did not reveal a statistically significant association between IVF treatment and ASD compared to spontaneous conception. Interestingly, they did find an increased risk of ASD with progesterone hormone treatment, but hormone treatment on its own does not fall under ART as defined by the CDC [6] since it does not involve the handling of eggs or embryos. Similarly, though Bay et al. [83] found no increased risk of mental disorders with IVF or ICSI treatment, they observed an increased risk of mental disorders, especially ASD and tic disorders, in children born after ovulation induction with or without insemination. Berrada et al. [84] found a statistically significant, though small, increased risk for ASD and Tourette Syndrome, a neuropsychiatric disorder characterized by motor and phonic tics, with IVF. Though no associated ASD risk was found with IVF treatment in Sandin et al.'s [57] study, they did observe a small but statistically significant increased risk of mental retardation. Given the conflicting results regarding the association between IVF and ASD, as well as other neurological complications, more study is warranted.

3.3. Intracytoplasmic Sperm Injection

ICSI is often the first choice of ART for male infertility [60]. Since the spermatozoa are sparse with little motility in these cases, ICSI offers a controlled procedure in which only one sperm is microinjected into an oocyte to induce fertilization [5]. IVF can be used with or without ICSI, but for comparison, IVF alone utilizes between 50,000 and 100,000 sperm as opposed to the single sperm used in ICSI [5]. This gives couples struggling with male infertility a feasible avenue for treatment. However, ICSI has been associated with increased sperm DNA damage [85], higher frequency of chromosomal abnormalities in somatic cells and spermatozoa [86], and adverse neurodevelopmental outcomes in offspring such as increased risk for ASD and intellectual disability compared to conventional IVF [30] (Table 3).

Table 3. Effects of ICSI on neurodevelopmental outcomes in children.

Study Design	Sample Size	Country	Specific Neurodevelopmental Outcome (s)	Results	Source
Cohort study	1,575,971 singleton births	Taiwan	ASD	Increased risk with ICSI	Lo 2022 [85]
Meta-analysis	10 studies (8 cohort studies, 2 case-control studies)	Denmark Western Australia America Finland Sweden	ASD, CP, intellectual disability, behavioral problems	Increased risk of ASD and intellectual disability with ICSI compared to IVF No increased risk of CP	Djuwantono 2020 [30]
Comparative study	ICSI: 87 children IVF: 92 children NC: 85 children	The Netherlands	Behavioral disorders, ASD, Problem behavior	Results inconclusive Higher risk of ASD with ICSI	Knoester 2007 [87]
Active surveillance	6245 children	USA	ASD	Positive correlation	Maenner 2023 [88]
Population-based, prospective cohort	11,514 ICSI conceived infants	Sweden	ASD, mental retardation	Increased risk of ASD and mental retardation No significant correlation with singletons	Sandin 2013 [57]
Systematic review and meta-analysis	19,462 children in meta-analysis 41 studies (2 case-control studies, 39 cohort studies)	Denmark Sweden Finland Israel Croatia Australia Singapore Italy Greece Great Britain Japan Belgium The Netherlands Germany	CP, ASD, developmental delay	Increased risk of CP Inconsistent results regarding ASD and risk of developmental delay	Hvidtjørn 2009 [89]

Table 3. *Cont.*

Study Design	Sample Size	Country	Specific Neurodevelopmental Outcome (s)	Results	Source
Population-based retrospective cohort	42,383 children	USA	ASD	Higher risk with ICSI	Kissin 2015 [90]
Population-based cohort	1,370,152 children	Canada	ASD	Increased risk of ASD with OI/IUI and IVF/ICSI Slightly higher with OI/IUI	Velez 2023 [15]
Literature review	7 studies on cognitive outcomes 4 studies on neurodevelopmental outcomes (large population registry studies)	United Kingdom Sweden Australia Belgium Denmark Greece USA	Cognitive outcomes, ASD, mental retardation	No association with cognitive outcomes with ICSI Inconsistent results, some studies identified high risk of ASD and Mental retardation with ICSI	Rumbold 2019 [91]
Prospective longitudinal cohort study	103 children	The Netherlands	Behavioral, cognitive, motor performance, and physical development after ICSI	Slight increased risk of ASD (2 children diagnosed)	Meijerink 2016 [92]
Narrative review	8 studies (3 cohort, 3 population-based registry studies, 1 systematic review, 1 meta-analysis)	The Netherlands Australia Denmark Sweden USA	Psychomotor development, IQ, mental retardation, ASD, CP	No differences in psychomotor development Lower IQ scores in ICSI singletons Increased risk of mental retardation in ICSI singletons Increased risk of ASD in ICSI singletons	Bergh 2020 [34]
Comparative analysis	4 males	China	ASD	ICSI using manually selected spermatozoa higher risk of ASD in offspring	Wang 2021 [93]
Comparative analysis	ICSI: 1914 questionnaires IVF: 451 questionnaires	USA	Development and behavior	No differences in child behavior between ICSI and IVF cohorts. ICSI from ejaculated spermatozoa had high risk of abnormal development and behavior compared to surgically removed spermatozoa	Cheung 2021 [81]

Table 3. *Cont.*

Study Design	Sample Size	Country	Specific Neurodevelopmental Outcome (s)	Results	Source
Systematic review	34 studies (18 prospective cohorts, 7 cross-sectional cohorts, 11 retrospective cohorts)	Belgium Denmark Greece Sweden United Kingdom Germany Holland Australia Iran USA Finland Spain China Israel	ASD	Higher risk of ASD in ICSI conceived children	Catford 2017 [94]
Longitudinal cohort	3904 children	USA	ASD	No increased risk	Diop 2019 [45]
Literature review	50 studies	Not specified	Cognitive, motor, and language development, behavioral problems	ICSI children found to have higher risk of ASD than the general population	Zhan 2013 [37]
Prospective register-based cohort	SC: 555,828 IVF/ICSI: 14,991 OI/IUI: 18,148	Denmark	Mental disorders	No increased risk with IVF or ICSI Small increased incidence with OI and IUI	Bay 2013 [83]

Abbreviations: IVF, in vitro fertilization; ICSI, intracytoplasmic sperm injection; ASD, autism spectrum disorder; CP, cerebral palsy; OI, ovulation induction; IUI, intrauterine insemination; SC, spontaneously conceived.

More recently, concerns have been raised about ICSI because of the rising incidence of both the use of this assistive reproductive treatment and ASD among the general public. There have been concerns over ICSI's potential effect on the development of ASD, with particular interest on the process of inserting the sperm, which may physically damage the egg and contaminate the cytoplasm of the egg cell with culture media [57], including additives to decrease mobility like polyvinylpyrrolidone [95]. The selection process of the sperm may increase oxidative stress and cause damage to DNA, possibly due to temperature, gas concentration used, and pH, all of which may increase stress to sperm and oocytes [85]. The selected sperm may also carry genetic abnormalities such as Y-chromosome microdeletions and Cystic Fibrosis mutations [96].

The association between ICSI and ASD remains highly controversial, with studies reporting contradictory findings. Due to conflicting evidence, it is challenging to reach a conclusion about whether ICSI directly contributes to the development of ASD in children conceived via ART. A few literature reviews found an increased risk of ASD among children born through the use of ICSI technology [37,94]. Other literature reviews also reported increased risk of ASD as well as mental retardation in ICSI-conceived children, though they contained several studies with inconsistent results [34,91]. Knoester et al. [87] found that ASD was identified in 3 out of 87 (3.4%) children born through the use of ICSI. The CDC reported that 2.8% (1 in 36 children) of 8-year-old children in 2020 were diagnosed with ASD [88]. Knoester et al.'s findings [87] show a higher percentage than the reported incidences of ASD in the general population. However, due to the small sample size, there is a need for larger cohort studies to thoroughly investigate the associations between ICSI and ASD.

A statistically significant increase in the risk of ASD was found in a study that examined the effects of ICSI using fresh embryos and surgically removed sperm compared to traditional IVF treatments [57]. In a study that focused on the type of spermatozoa used, a higher risk of abnormal behavior and development was seen in children born after ICSI treatments that used ejaculated spermatozoa compared to surgically extracted spermatozoa [81]. Another study comparing zona pellucida bound spermatozoa and manually selected spermatozoa observed differences in their methylation profiles which were enriched in autism genes, though it is important to note the study's small sample size of only four men [93]. A more recent study by Lo et al. [85] reported increased risks of ASD and developmental delay in children from ART with ICSI compared to natural conception. Though the authors were unable to explain the role of male infertility in their findings, they still highlight the potentially major increased neurological risk that ICSI imposes. In Denmark, Hvidtjørn et al. [89] conducted a population-based study that tracked children for four to thirteen years after they were born through assistive technologies. Procedures such as in vitro fertilization and ovulation induction with or without subsequent insemination were included in this study in addition to ICSI. According to their findings, children born following assisted conception did not have a higher risk of ASD. Another population-based cohort in Canada found an increased risk of ASD in IVF- and ICSI-conceived children, although the risk was higher in children conceived through ovulation induction and intrauterine insemination [15]. A larger study conducted in California revealed that children conceived with ICSI had an increased risk of ASD during the first 5 years of life [90]. Conversely, other studies are reassuring regarding effects of ICSI on development [92], and Diop et al. [45] reported no increased risk of ASD diagnosis in ICSI-conceived children compared to those born to fertile women. In considering the conflicting findings, Briana and Malamitsi-Puchner [27] have recommended restricting the use of ICSI to male-factor infertility cases until there is more conclusive evidence available. They point out the necessity for larger prospective cohort studies, as well as further exploration of underlying molecular mechanisms, to substantiate associations between ICSI and ASD.

Epigenetic alterations have been considered in ICSI as animal studies have shown more of these changes with ICSI compared to IVF, with ICSI affecting gene transcription and methylation of some epigenetically regulated genes [60]. It is important to note that the increase in ASD and other epigenetic malformations cannot all be attributed to ICSI application, but paternal conditions as well [97]. Studies not only link ICSI to ASD but to other epigenetic disorders, chromosomal abnormalities, congenital malformations, and general neuropsychological development [27]. The results of one study that aimed to address whether ICSI or conventional IVF should be the recommended treatment option for male factor infertility cases suggested that the fertilization rate per oocyte was significantly higher with ICSI, but implantation and clinical pregnancy rates were marginally higher with IVF [98]. Their conclusion was that IVF should be the recommended treatment, as ICSI bypassed more natural processes such as natural sperm selection, was associated with chromosomal abnormalities [99], and increased incidence of ASD [90]. They ultimately recommended IVF as the preferred treatment option for male-factor infertility due to its lower cost and greater accessibility.

3.4. Fresh vs. Frozen Embryo Transfer

The practice of frozen embryo transfer has commonly been used in tandem with IVF and ICSI. Cryopreservation allows for long-term storage of gametes and embryos so that they may be used at a later time. However, there has been scrutiny as to whether cryopreservation affects physical development [100]. Despite this information, there are relatively few reviews that have assessed neurodevelopmental effects of cryopreservation and frozen embryo transfer and its relationship with ASD (Table 4). A meta-analysis reviewing criteria for successful IVF treatments found that cryopreservation alongside IVF led to improved outcomes, with higher ongoing pregnancy rates [101]. Other studies have concluded that the use of frozen embryos would be beneficial for patients who have

previously undergone failed fresh embryo cycles [102]. However, the analysis of using frozen embryos and its relationship with ASD is still relatively limited. A study that observed the relationship and quality of IVF and ICSI determined that these procedures increase the risk of ASD; however, it failed to include data on whether embryos were fresh or frozen [55].

Table 4. Effects of fresh vs. frozen embryo transfer on neurodevelopmental outcomes in children.

Study Design	Sample Size	Country	Specific Neurodevelopmental Outcome (s)	Results	Source
Prospective register-based cohort	33,139 ART-conceived children 555,828 SC children	Denmark	Mental disorders	No significantly increased hazards associated	Bay 2013 [83]
Population-based cohort	108,548 children 83,452 parents	Israel	ASD	No statistically significant association	Davidovitch 2018 [12]
Meta-analysis	10 studies (8 cohort studies, 2 case-control studies)	Denmark Western Australia America Finland Sweden	ASD, CP, intellectual disability, behavioral problems	No significant differences in risk between fresh vs. frozen embryo transfer	Djuwantono 2020 [30]

Abbreviations: ART, assisted reproductive technologies; ASD, autism spectrum disorder; CP, cerebral palsy; SC, spontaneously conceived.

Pregnancy and delivery rates are higher for frozen embryo transfer than for both IVF with fresh embryo transfer and ICSI according to the European IVF-Monitoring Consortium (EIM) for the ESHRE [76]. This was also found in Nardelli et al. [64], which showed use of frozen in comparison to fresh embryos results in higher ongoing pregnancy rates for patients who underwent IVF. Another study found there was a lower percentage of infants diagnosed with autism who originated from frozen or thawed embryos, but did not mention whether these embryos were associated with another ART procedure; the study did not include whether these embryos were also obtained via ICSI due to missing data [90]. A relevant study showed no hazard risk associated with the use of frozen embryos when it came to mental disorders [83]. Of those reviewed, only two papers concluded that the use of fresh or frozen embryos did not significantly affect the outcomes of IVF [12,43]. This is to say, from the information that currently exists, one could cautiously conclude that the state of the embryo during transfer is not responsible for ASD. However, given the limited data available, more studies are required to conclude whether cryopreservation alone, or the treatments it is paired with, increases the risk of ASD.

When compared to other procedures, the use of frozen embryos does not appear to contribute to ASD prevalence in offspring. However, there are limited studies observing the use of cryopreservation alone, and therefore more studies are needed to determine if it does affect offspring. More studies are required to determine if this is a distinguishing feature that will lead to ASD development in children.

4. Discussion

In this review, we examined the literature regarding the relationship between ART and neurodevelopmental disorders, specifically autism spectrum disorder. The findings vary widely between studies and there is a lack of strong evidence to suggest that ART is an independent risk factor for ASD. Importantly, Gullo et al. [31] highlight that the main alterations of the central nervous system involved in the pathogenesis of neurodevelopmental disorders are attributed to errors in neuronal migration. Since these events occur during fetal development, this suggests that the mode of conception may not play as crucial a

role in these pathologies. Nevertheless, adverse neurological outcomes in ART-conceived offspring have occasionally been identified, necessitating further investigation.

A common theme discussed throughout the literature regarding ART and its health implications is the presence of many confounding factors. Perhaps the most obvious risk associated with ART is multiple and preterm births, given the incidence of multiple embryo transfer. A Massachusetts Outcome Study of Assisted Reproductive Technology (MOSART) study by Luke et al. [20] identified multiple births as the primary factor associated with adverse birth outcomes in the context of ART. Plurality, which does increase risk for ASD, was compared with several other risk factors including semen source, assisted hatching, number of embryos transferred, and ICSI, all of which showed little or no significant impact on birth outcomes. Other studies have shown an increased risk for ASD among multiple births but not for singleton pregnancies in patients with a history of infertility or use of infertility treatments [103]. This risk appears to result from an interaction between infertility or infertility treatments and multiple births, as there is likely no relationship between ASD and naturally acquired multiple births [104,105]. Because of this, there has been a move towards single embryo transfer, which decreases the risk for neurodevelopmental disorders in offspring [52]. Although there is greater evidence of adverse birth outcomes with multiple pregnancies, there are still risks associated with ART singleton pregnancies, such as preterm birth, low birthweight, and perinatal mortality [60,106,107].

Advanced parental age is a known risk factor for ASD [108], and women are often at an advanced age when they begin seeking infertility treatment. Thus, the pregnancy may already be at an increased risk for fetal and neonatal abnormalities [28] regardless of the mode of conception. Studies have shown that increased paternal and maternal age is significantly associated with autism-associated copy number variants (CNVs) in ART-conceived offspring [43].

In addition to advanced age, patients utilizing ART are more likely to have underlying infertility, some causes including endometriosis, polycystic ovarian syndrome (PCOS), other ovulatory disorders, uterine factor, tubal factor, male factor, and diminished ovarian reserve [109]. Taking this into consideration, the question remains whether factors related to infertility lead to adverse outcomes or the ART treatment itself. Another MOSART study by Stern et al. [109] found that ART further increases the risk of adverse outcomes in pregnancies and deliveries compared to subfertility/infertility alone. As previously mentioned, a study by Grether et al. [103] found an increased risk for ASD with infertility history and infertility treatments, but only among multiple births and not singletons.

Maternal hormone imbalances are another significant risk factor for ASD [110]. During critical periods of brain development, fetal steroid hormones may exert an epigenetic fetal programming mechanism for autism [111]. Progesterone has been shown to impair the development of cognitive responses by downregulating the expression of ERβ, an estrogen receptor [110], and disrupt myelination through the peripheral and central nervous systems [112]. It has been postulated that the increased risk of developing ASD seen with progesterone exposure in some studies [12,111,113] may be due to epigenetic modifications during critical periods of development. Though hormone treatment alone does not fall under the CDC's definition of ART [6], fertility hormone therapies used in conjunction with other types of ART should be further investigated.

As discussed, there are many confounding factors to consider when assessing the impact of ART on adverse outcomes in offspring. In addition to those explored here, other demographic factors remain, such as race/ethnicity, education, marital status, and insurance type, that may impact health outcomes in the context of ART [62]. Interestingly, one study still noted an association between ASD and ART even after controlling for various confounding factors [114]. As such, further research is needed to confirm whether these factors and other factors are wholly responsible for the sometimes-observed relationship between ASD and ART before a clear conclusion can be drawn.

While in-depth, long-term studies on the mechanisms underlying ART effects are limited in humans, animal studies have proven valuable as they provide large sample sizes

while controlling some of the confounding factors that are often involved in humans [115]. In Duranthon et al.'s [115] review of animal studies, ART-associated procedures impact short-term (blastocyst stage) and long-term (feto-placental, peri and postnatal) development, with postnatal effects on birth weight and growth trajectories, metabolic and cardiovascular health, behavior, and epigenetics. For instance, IVF in particular alters the expression of imprinted genes that have a major role in normal animal development [116].

Regarding neurological outcomes and behavior specifically, several animal studies have assessed the risk of ART-associated procedures, most using mouse models (Table 5). In one such study, a BTBR mouse strain was used as an idiopathic model of ASD and compared to a control strain (C57BL/6J) after in vitro culture and embryo transfer [117]. The authors found that females of both strains exhibited decreased social recognition. Increased anxiety as well as depressive-like behavior were seen in the offspring of mice that underwent either IVF and embryo transfer or IVF and frozen-thawed embryo transfer when compared to the naturally conceived group [118]. Similarly, increased anxiety-like behavior was found in the offspring of superovulated mice [119]. A study assessing ischemia/reperfusion brain injury in ART-conceived mice reported significantly worse morphological and functional stroke outcomes in addition to worse neurological performance at 24 and 48 h after artery occlusion [120]. While behavioral changes in ART-conceived mice have been observed, a few studies assessing memory and learning reported no significant differences [119,121]. ART-conceived Rhesus monkeys demonstrated normal development, including neonatal reflexes, self-feeding ability, recognition, and memory [122]. Interestingly, monkeys conceived via embryo splitting and ICSI displayed accelerated attainment of milestones involving sensory-motor behaviors.

Table 5. Effects of ART, embryo biopsy, and culture medium on neurodevelopmental outcomes in animal models.

Species	Exposure	Sample Size	Specific Neurodevelopmental Outcome (s)	Behavior Test Used	Results	Source
Mice	Blastomere biopsy of in vitro cultured four-cell embryos	Control $n = 10$ Biopsied $n = 7$	Spatial learning	Hidden platform version of the MWM, pole climbing test	Poorer spatial learning ability, increased neuron degeneration, and altered expression of proteins involved in neural degeneration	Wu 2014 [123]
Mice	Blastomere biopsy of in vitro cultured four-cell embryos	Control $n = 8$ Biopsied $n = 5$	Intelligence and memory	Hidden platform version of the MWM	Behavioral defects associated with increased hypomyelination of nerve fibers	Yu 2009 [124]
Mice	Embryo transfer following culture in vivo (control), in KSOM, or in Whitten's medium	In vivo (control): $n = 34$ KSOM: $n = 47$ Whitten's medium: $n = 46$	Anxiety, spatial learning, motor performance	Elevated zero maze, hidden platform version of the MWM, Rota-rod, classical fear conditioning tests	Reduced anxiety, decreased memorization of spatial information, and increased locomotor activity compared to controls	Ecker 2004 [125]
Mice	Embryos obtained from superovulated females exposed to either: 1. KSOM + 10% FCS 2. KSOM + 1 g/L BSA (control)	−FCS: $n = 35$ +FCS: $n = 43$	Hyperactivity, anxiety, implicit memory	Open field, elevated plus maze, free-choice exploration in Y-maze tests	Altered locomotion activity at 5 and 15 months in +FCS group Increased anxiety and deficiencies in implicit memory in +FCS group	Fernández-Gonzalez 2004 [126]

Table 5. *Cont.*

Species	Exposure	Sample Size	Specific Neurodevelopmental Outcome (s)	Behavior Test Used	Results	Source
Mice: C57BL/6J (controls) and BTBR (idiopathic model of ASD)	In vitro culture and embryo transfer	C57BL/6J: 39 males 47 females BTBR: 35 males 44 females	Social behavior	Open field, social motivation and recognition tests	Decreased social recognition in females of both strains	Rozhkova 2023 [117]
Mice	IVF, embryo culture, and embryo transfer; ischemia/reperfusion brain injury	Control: $n = 5$ ART: $n = 7$–10	Neurological performance post-stroke	Composite sensory-motor test	Significantly worse morphological and functional stroke outcomes Worse neurological performance 24 h and 48 h after artery occlusion	Bonetti 2021 [120]
Mice	Superovulation	Control: $n = 25$ Superovulated: $n = 23$	Anxiety, learning and memory, depressive behavior, cortical neuron density	Elevated zero maze, open field, novel object recognition, forced swim tests	Increased anxiety-like behavior No differences in learning and memory Fewer neurons per field	Mainigi 2015 [119]
Mice	IVF-ET, IVF-FET	Control: $n = 7$ IVF-ET: $n = 7$ IVF-FET: $n = 7$	Anxiety, spatial learning and memory, depressive behavior	Open field, elevated plus maze, MWM, light/dark transition, tail suspension, forced swim, sucrose preference tests	Increased anxiety and depression-like behaviors seen in the IVF-ET and IVF-FET groups compared to NC group	Qin 2021 [118]
Rhesus Monkey (*Macaca mulatta*)	Embryo splitting, ICSI, IVF, and AI	28 rhesus monkey infants	Neonatal reflexes, self-feeding ability, recognition and memory, object concept attainment, simple discrimination learning and reversal, learning set acquisition	Reflex and sensory motor response, self-feeding, recognition memory, WGTA series, object concept physical-search tests	No delayed development in ART group Accelerated attainment of milestones involving sensory-motor behaviors seen in ES and ICSI groups	Sackett 2005 [122]
Mice	IVF	NC: $n = 12$ (6 males and 6 females) IVF: $n = 12$ (6 males and 6 females)	Spatial learning and memory	Hidden platform version of the MWM	No effect on memory or learning ability	Li 2011 [121]

Abbreviations: MWM, Morris water maze; KSOM, K+-modified simplex optimized medium; FCS, fetal calf serum; BSA, bovine serum albumin; ASD, autism spectrum disorder; IVF, in vitro fertilization; IVF-ET, IVF and embryo transfer; IVF-FET, IVF and frozen-thawed embryo transfer; NC, naturally conceived; AI, artificial insemination; WGTA, Wisconsin General Test Apparatus.

Embryo culture media is of particular concern, as differences in composition have various effects on animal models [60]. In an article studying the effects of IVF using outbred mice, the authors found that use of suboptimal embryo culture conditions (Whitten's medium, 20% O_2) resulted in growth alterations, glucose intolerance, and enlarged left hearts in adult males when compared to optimal culture conditions (KSOM AA at 5% O_2) [127]. In mice, culture media also affects insulin resistance [128]; systolic blood pressure, serum angiotensin levels, and activity of hepatic enzymes involved in gluconeo-

genesis [116]; anxiety, memorization of spatial information, and locomotor activity [125]; and long-term memory [126]. While effects of culture medium have been more extensively studied in animals, some findings have been observed in humans. Bouillon et al. [129] found that embryos cultured in Global medium, compared to Single Step Medium (SSM), were significantly less likely to display developmental problems such as alterations in social skills, self-help, gross and fine motor skills, language comprehension, and expressive language. Though the differences in media composition cannot be fully explored as it is considered proprietary information, the authors note that SSM contains the amino acid taurine while Global does not, and the glutamine in both media is supplied by two different heat-stable di-peptides (Alanyl-L-Glutamine in SSM and Glycyl-L-Glutamine in Global).

Epigenetic regulation of gene expression is actively being investigated in the context of ART. In animals, superovulation, in vitro egg culture, and embryo manipulation lead to genetic alterations in the egg and embryo that affect pregnancy outcomes [116]. Furthermore, in mice, upregulation of a signaling protein that protects cells from oxidative stress was seen in both IVF blastocysts and in adult offspring muscle and fat [115]. This was associated with increased histone H4 acetylation at the promoter, demonstrating a link between epigenetic modifications in the embryo and in adult tissues. Mouse IVF embryos biopsied at the four-cell stage abnormally expressed proteins involved in neurodegenerative disease and displayed reduced methylation of promoters of genes associated with neural disorders [123,124]. Additionally, IVF placentas show altered global gene expression leading to an over-representation of biological pathways such as immune response, cell cycle control, and amino acid and cholesterol metabolism [130]. In a recent review by Schroeder et al. [131], the authors propose that irregularities in the structure and function of the placenta in the context of ART could potentially cause adverse effects in the long-term, highlighting the need for further study especially as ART-conceived children age.

Epigenetic processes have been implicated in the pathogenesis of many neurological diseases [132]. Epigenetic mechanisms in neurological disorders, development, and behavior were first discovered from studies on genomic imprinting, which is important in the control of placental function and brain development [133]. Defects in genetic imprinting are involved in neuropsychiatric disorders such as Rett and Fragile X syndromes, which are characterized by autism-like features in some patients [134]. Oxidative stress and abnormal DNA methylation have also been implicated in the pathophysiology of ASD, promoting cellular damage and altered epigenetic gene expression [134]. Furthermore, epigenetic changes can influence activation of immune responses involved in ASD susceptibility [135].

Regarding ART, epigenetic changes induced by repeated exposure to hormones, sperm preparation, freezing of embryos and gametes, use of culture media, embryo growth conditions, and delayed insemination have been suggested as potential mechanisms of ASD development [78,84]. Specifically with IVF, administration of gonadotropins during ovarian stimulation leads to elevated estradiol levels during critical periods of embryogenesis, potentially causing metabolic disturbances, and impaired implantation and placentation [78]. Other epigenetic risks associated with IVF have been described, such as methylation of imprinted genes and epigenetic changes in the placental methylome [136]. As discussed in a recent article by von Wolff et al. [136], there are still too few studies completed on a limited number of human IVF oocytes to draw any conclusions about epigenetic effects in humans. As such, mechanisms underlying the reported adverse outcomes in ART-conceived offspring need to be further elucidated.

4.1. Limitations

Our review poses several limitations. A large portion of studies reviewed in this paper originate from Europe and the U.S. which does not fully represent the global landscape of ART and ASD. Though a few mentioned here have been conducted in Asian, Israeli, Iranian, Australian, Indian, and Arabic populations, many more studies come from the Scandinavian countries, where country-wide databases and registries provide enough information and populations for study [137]. Additionally, we only included papers

written in English, which may have limited our access to studies about ART written by authors in other countries. The shortage of literature from other countries, which could also be due to database limitations and/or healthcare disparities, leaves out important demographic information that should be considered when assessing the impact of ART on a global scale. It is not entirely clear whether this issue simply represents regional differences in the use of ART or a bias in research. In support of the first possibility, a previous review of IVF in Asia and Africa found affordability to be a contributing factor to lower rates of ART procedures completed [138]. For example, the cost of fertility treatment is estimated to be at least double the monthly income for patients who reside in Rwanda [139]. Another study reviewing the efficacy of ART in sub-Saharan Africa cited the most prominent barrier to care was cost [140]. Upon review of costs between countries, regions located in the Eastern Mediterranean were found to offer more affordable ART than those in Asia and Africa [141]. Therefore, making ART more accessible on an international level would be an important goal in addressing these disparities. Another major contributing factor to lower ART utilization is the overall cultural attitude towards infertility and infertile individuals [142]. Having a diverse population included in future research would provide more information on the overall efficacy of ART, as well as how it relates to ASD and other health conditions.

Another limitation of our review is that the studies cited here are relatively recent publications representing a span of only 23 years. This is largely due to ART being a fairly new technology, in addition to there being a limited number of studies examining the relationship between ASD and ART. As previously mentioned, the first successful attempt at ART occurred in 1978 with the birth of Louise Brown [143]. Therefore, the long-term data on ART in terms of health outcomes is limited due to its relative novelty, as the oldest individuals conceived via ART are only now in their early 40's. Another important consideration is the higher utilization of IVF compared to other forms of ART, making the data on procedures like ICSI, GIFT, and ZIFT even more limited. Both GIFT and ZIFT, for example, account for less than 0.5% of all ART procedures in the U.S. performed in 2003, with the remaining ART procedures only consisting of IVF [144].

As the first generations of ART-conceived children reach later stages of life, researchers will gain a clearer picture of the long-term outcomes of these technologies. Longitudinal studies tracking health, psychological well-being, and social integration will provide valuable data, but these studies take time. The scope of this paper cannot predict the possible effects of ART, nor its association with neurodevelopmental disorders until further research is completed in the years to come. Until then, the challenge remains balancing the immediate benefits of ART with the responsibility to monitor and understand its long-term consequences.

4.2. Further Research

More research is needed to address the many remaining questions regarding the effects of ART on neurodevelopmental outcomes in offspring and potential mechanisms linking ART and ASD. Future studies in ART-conceived children should consider ASD diagnosis criteria and how the initial diagnosis was obtained. Importantly, there have been cases of children diagnosed with ASD earlier in life that later "lose" their diagnosis due to initial misdiagnoses or difficulties differentiating children with ASD from children with other developmental delays [145]. Of course, this is dependent on the initial diagnostic criteria of ASD used, whether the diagnosis is applicable to all patients, and whether the diagnosis criteria are internationally recognized as appropriate.

The patient population should also be considered, as ART is often accessed by affluent communities [141,146]. Possible differences in genetic makeup could predispose certain populations to ASD, potentially increasing the incidence of ASD in ART offspring. There is also a potential for individuals to become diagnosed with ASD later in life, possibly related to various socioeconomic factors that may influence development over time [147]. Therefore, the current data is limited to those patients that have access to ART.

Ethical considerations are also involved. Do the benefits of being able to conceive, a privilege not afforded to everyone, outweigh the associated risks of ART? Would knowing these risks deter patients who are good candidates for ART and prevent them from seeking personalized treatment options? Moving forward, we hope that studies clarify and illuminate the true risks associated with ART and weigh this against the value it can bring to patients struggling with infertility so that they can make well-informed decisions before proceeding with treatment.

5. Conclusions

Many studies suggest a relationship between ART and risk of ASD. However, after a thorough review of the literature, it is still unclear whether adverse neurodevelopmental outcomes in ART-conceived offspring, such as increased risk of developing ASD, are related to the ART procedures themselves or to other factors such as maternal age, underlying infertility, and multiple and preterm births. Other confounders to consider include socioeconomic status, race, genetic and/or environmental factors, laboratory methodologies including the composition of embryo culture media, or a combination of these; which complicates things further. Thus, more research is necessary to determine the true impact of ART on offspring. Based on the overwhelming majority of studies reviewed, the results are reassuring thus far and suggest that, while some risks exist, ART is generally a neurodevelopmentally safe option for couples wishing to conceive.

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