

Association Between Assisted Reproductive Techniques and Autism Spectrum Disorder

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Received: January 25, 2022; **Published:** February 25, 2022

Abstract

The aim of this review was to examine the possible association between assisted reproductive techniques, such as IVF and autism spectrum disorders. The method used is a review from recently published research where risk ratios (Relative Risks-RRs) and 95% confidence intervals (95% CI) were used to calculate and analyze the strength of the correlation using fixed or random outcome models based on heterogeneity test based on aggregate, and subgroup analyzes. In addition, group analyses were examined based on each study's design, location, and quality, while some studies showed a statistically significant correlation. In a few cases, it was shown that IVF could lead to a higher probability for ASD.

Keywords: Autism Spectrum Disorder; ASD; Fertilization; IVF; ART; Autism; Pregnancy; Child

Introduction

Autism Spectrum Disorder (ASD) is a neurodevelopmental disorder with disturbances in socialization and, combined with limited and tedious behavior [16]. Despite the great effort made to treat ASD, it remains a significant public health problem worldwide. ASD risk assessments have increased rapidly in the last decades [1]. Recent estimates suggest that ASD will occur in 1 out of 68 U.S. children under the age of 8, with a rapidly increasing incidence over the past decade [15].

Numerous studies [3,4,6] searched for the reasons and associated autism with early birth, lower birth weight, and family characteristics, like high social and economic status, education, old father or mother, Caucasian race, and history of psychiatric conditions connected with ASD. Furthermore, exists a big and compound genetic background with a smaller set of familiar ASD cases and an essential role for seldom and usual variants of copy numbers.

Even though the cause of ASD is still undetermined, it is regarded multifactorial and includes environmental factors and genetic as well. Therefore, the early diagnosis of ASD by identifying its causes is considered necessary [1].

Gao, *et al.* [4] study aimed to investigate the modifiable environmental factors that increase the risk of ASD. From all those endanger elements, assisted reproduction technology has been studied a lot due to its popularity. This technology, described as *In vitro* fertilization (IVF) and other alike course of actions, has been associated with increased rates of ASD [3]. In a typical assisted reproduction techniques

procedure, oocytes, and sperm from donors or one or both parents are merged in a fertilization lab and are grown for many days before implantation. Hormone medication is often used to enhance or regulate ovulation. There is a number of variants, like injecting sperm directly into the oocyte, and less standard methods, where the fertilized embryo is placed in the uterus. Multiple embryos are often transferred to maximize the chance of implantation and pregnancy, leading to a high rate of multiple pregnancies and a higher order than ART. To decrease the occurrence of multiple births, the guidelines published by the Society for Assisted Reproductive Technology and the American Society for Reproductive Medicine state that no more than 2 (or 3 in certain cases) embryos should be transferred to patients in a single procedure [3].

The use of ART increased the overall danger of congenital malformations by almost 30%, with about twice the risk of developing nervous system disorders [4].

Data showed that ART could lead to a higher risk of genetic mutations or preterm birth and low birth weight and genetic mapping disorders, which might lead to the appearance of autism. Many epidemiological and observational studies have investigated the relationship between ART risk and ASD in offspring, but the results were inconsistent [4].

The aim of this essay is to explore the relationship between IVF and ASD based on various research.

Methodology

The literature review that was followed is part of the systematic literature review and the process of meta-analysis [14] containing two basic research parameters, the development of the research questions and the development of the research process. Our research process was based on the following research question:

RQ1: Does IVF lead to the birth of children on the autism spectrum?

The research material was collected through the PRISMA (Preferred reporting items for systematic review and meta-analysis). Then the process was defined based on the present methodology. The development of the PRISMA methodology refers to 27 specific points, which leads to its proper use. These points are 1) Identification of the method followed, systematic literature review, meta-analysis or both. In the present study, only a systematic literature review was performed; 2) Presentation through a detailed summary of the research objectives, sources, selection criteria, participants based on research articles, results and limitations; 3) The next step was the analysis where various variables were extracted which were statistically analyzed for the best and most objective extraction of the final results. Finally, the results were discussed, and the final findings were presented.

PubMed, Scopus, ScienceDirect, and Google Scholar were used as research bases and research tools. The keywords used to extract the articles were “spectrum autism disorder and IVF”. There were 100 articles in total which were rated as relevant, and 15 were selected. The selection criteria of the articles were the following: articles absolutely on the subject, articles written in English, articles that the subject had full access to.

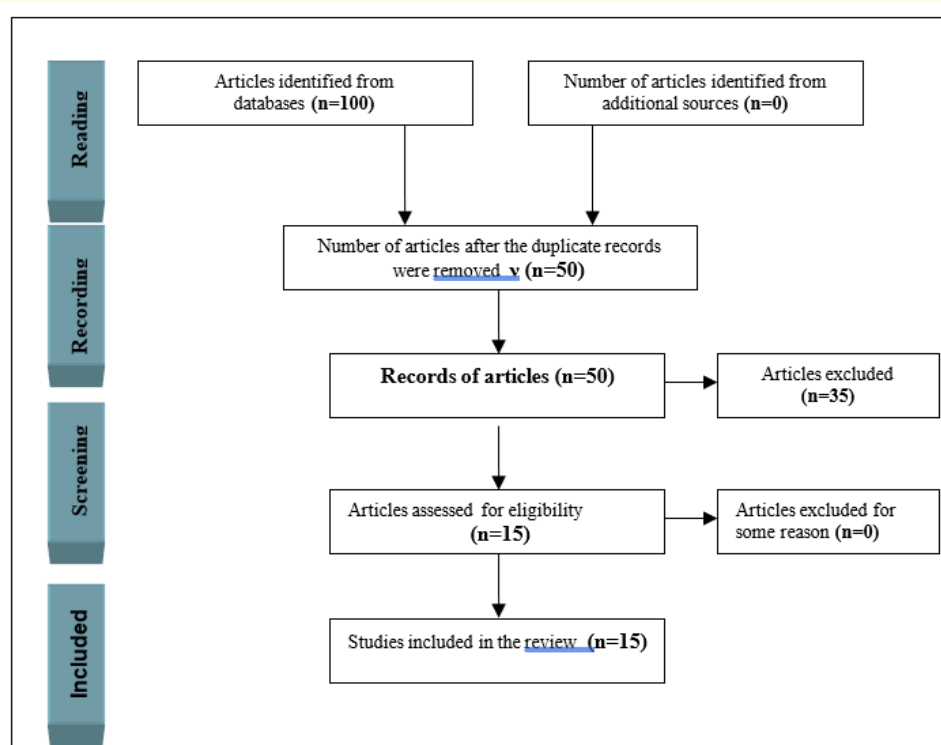


Figure 1: Provides a graphical representation of the article selection process.

	Authors	Title	Results
1	Ericson., et al. [2]	Hospital care utilization of infants born after IVF	There was no significant correlation between IVF and ASD.
2	Fountain., et al. [3]	Association between assisted reproductive technology conception and autism in California, 1997–2007	The association between ART and autism is primarily explained by adverse prenatal and perinatal outcomes and multiple births.
3	Gardener., et al. [5]	Prenatal risk factors for autism: a comprehensive meta-analysis	Various perinatal factors have been suggested to increase the risk of autism spectrum disorders (ASD), including maternal prenatal medication use, early life, growth retardation, endosomal hypoxia, and bleeding.
4	Hansen., et al. [7]	Assisted reproductive technologies and the risk of congenital disabilities—a systematic review	In vitro fertilization fetuses are associated with an increased risk of perinatal problems, such as preterm birth, perinatal mortality, low birth weight, young gestational age and neonatal intensive care, and congenital anomalies.
5	Helmerhorst., et al. [8]	Perinatal outcome of singletons and twins after assisted conception: a systematic review of controlled studies	IVF fetuses are associated with an increased risk of perinatal problems, such as premature birth, perinatal mortality, low birth weight, young gestational age and neonatal intensive care
6	Hvidtjorn., et al. [10]	Cerebral palsy, autism spectrum disorders, and developmental delay in children born after assisted conception: a systematic review and meta-analysis,	Children of IVF have an increased risk of cerebral palsy and other neurological problems
7	Hvidtjorn., et al. [9]	Risk of autism spectrum disorders in children born after assisted conception: a population-based follow-up study	No significant correlation was observed between IVF and ASD.
8	Klemetti., et al. [11]	Complication of IVF and Ovulation Induction	There was a low risk of complications after each IVF treatment cycle, repeated attempts resulted in serious complications for many women, and these occurred much more often than after ovulation induction alone.
9	Kolevzonet., et al. [12]	Prenatal and perinatal risk factors for autism: a review and integration of findings	Various perinatal factors have been suggested to increase the risk of autism spectrum disorders (ASD), including maternal prenatal medication use, premature life, growth retardation, endosomal hypoxia, and bleeding.

10	Lehti, et al. [12]	Autism spectrum disorders in IVF children: a national case-control study in Finland	No correlation was found between IVF and ASD or ASD subtypes.
11	Malmberg and Vaeth [17]	Do children born after assisted conception have less risk of developing infantile autism	Significantly lower risk (OR: 0.37, 95% CI: 0.14-0.98) of childhood autism in children born after ART than children who were naturally conceived.
12	Middelburg, et al. [18]	Neuromotor, cognitive, language and behavioral outcome in children born following IVF or ICSI-a systematic review	Because IVF babies are often followed only during perinatal or infant periods, there is less information about their well-being in later life. The effects of IVF are mediated by the risk of factors such as premature birth
13	Rimm, et al. [19]	A meta-analysis of controlled studies comparing significant malformation rates in IVF and ICSI infants with naturally conceived children	In vitro fertilization fetuses are associated with an increased risk of perinatal problems, such as preterm birth, perinatal mortality, low birth weight, young gestational age and neonatal intensive care, and congenital anomalies.
14	Sandin, et al. [20]	Autism and mental retardation among offspring born after in vitro fertilization	In total, 103 out of 6959 children born after IVF (1.5%) had ASD and 180 out of 15,830 (1.1%) were mentally retarded.
15	Wagenaar, et al. [21]	An overview of studies on early development, cognition, and psychosocial well-being in children born after in vitro fertilization	Because IVF children are often followed only during perinatal or infant periods, there is less information about their well-being in later life.

Table 1: Article selection process using the PRISMA method.

Results

ARTs are constantly evolving, and the number of newborns after IVF is growing. The course of pregnancy during IVF along with babies' health after IVF are of significant interest to public health. *In vitro* fertilization, embryos are connected with a higher danger of perinatal problems, like preterm birth, perinatal mortality, lower birth weight, and intensive care infants [8]. as well as congenital anomalies [7,19]. Because IVF children are usually monitored during perinatal or infant periods, not adequate information is provided about their health as growing up [18,21]. However, a number of studies with satisfactory follow-up time have manifested an enlarged danger of cerebral palsy and other neurological problems [10]. Various perinatal factors have shown that increase the danger of (ASD), including maternal prenatal medication use, premature life and growth retardation [5,12]. The study did not report different types of ASD separately. In addition, the study had a relatively short follow-up time. Because the follow-up time was only about four years (or a little more) it was not long enough to detect every case, as Asperger syndrome which is usually diagnosed later. Studies conducted in the United Kingdom, which diagnosed children with Asperger syndrome in the 1990s and 2000s, showed that the average age of diagnosis was between seven and ten

years old. There is one cohort study where a significant positive correlation was found between IVF and ASD [odds ratio-OR ratio: 1.68, 95% confidence interval (CI): 1.11-2.53] was based on the Finnish cohort [11], but the result was even less accurate than in the previously mentioned studies.

The main goal of Lehti, *et al.* [13] was to respond to the research question of whether an IVF increases the risk of ASD. According to the study results, no correlation was found between *In vitro* fertilization (IVF) and ASD or its subtypes. In particular, specific prenatal factors could enlarge the danger of ASD. *In vitro* fertilization increases the danger of perinatal problems, but most are associated with multiple pregnancies.

Sandin, *et al.* [20] conducted a study to investigate the relation between the use of any and /or different IVF methods and the danger of ASD and mental retardation in children. According to the study results, for more than 2.5 million newborns, 30,959 (1.2%) were born by IVF and followed for an average of 10 (SD, 6) years. In total, 103 out of 6959 children born after IVF (1.5%) had ASD and 180 out of 15,830 (1.1%) were mentally retarded. The R.R. for the ASD after any methods compared to spontaneous conception was 1.14 (95% CI, 0.94-1.39, 19.0 versus 15.6 per 100,000 person-years). ASD's RR was 1.18 (95% CI, 1.01-1.36, 46.3 versus 39.8 per 100,000 person-years). For both results, there was no statistically significant correlation when the analysis was limited to singletons.

Compared to IVF without ICSI with new embryo transfer, there was a statistically remarkable grown danger of ASD after ICSI using extracted sperm and fresh embryo (R.R., 4.60 [95% CI, 2.14-9.88], 135, 7 versus 29.3 per 100,000 people- years). Also, statistically remarkable danger of mental retardation occurred after ICSI using extracted sperm and fresh embryo). This was followed by the ICSI technique using insemination and fresh embryos (R.R., 1.47 [95% CI, 1.03-2.09], 90.6 versus 60.8 per 100,000 person-years).

After limiting the analysis to singletons, the danger of ICSI related to ICSI using extracted sperm were not important, although the danger related to ICSI with frozen embryo were remarkable for mental retardation relative risk -R.R., 2, 3680.0 versus 50.6 per 100,000 man-years).

Spontaneously compared, IVF method as a whole was not related to ASD but to mental retardation (statistically there is a remarkable increased danger. Moreover, for specified methods, IVF with ICSI for paternal infertility was related to a slight increase in R.R. for ASD and mental retardation than IVF without ICSI. Those disorders did not have a remarkable prevalence, and the growth of the total danger related to IVF was slight.

According to Fountain, *et al.*, ART-derived pregnancies share many of the correlations of autism, including older parents. Furthermore, the ART method adds to the pre-existing trend of older parents, pushing the upper limit of the fertile age range. Some studies have searched for the link between ART and the danger of ASD and other cognitive delays. However, the results are mixed and vague [3].

Fountain, *et al.* [3] reviewed the data on the ART-ASD relationship and found no consistency on the t results. Studies examining the results of ART failed to collect data from participants older than two years. Since autism can sometimes be diagnosed when a child is over four years old, this could be a problem. One case study proved that there is not any relation, although there was a slight indication of an association between light forms of ASD and artificial insemination. Another study of autistic children found no association with autism among children from ART.

Fountain, *et al.* [3] calculated the possible relation between ASD and ART in a ten-year cohort of kids in California. The researchers found an increased incidence of diagnosed autism among children from ART in the general population and between subgroups separated by proliferation, parity, infant sex, age and education of mother and father. At the population level, children from ART in California were more than twice as likely to develop autism than children from non-ART children. After adjusting for demographics and other factors re-

lated to ART and ASD, this enlarged rate was still statistically important for kids with mothers under the age of thirty-five. The increased incidence may be due primarily to the higher incidence of unwanted pregnancies and labor outcomes, including multiple births [3].

Population studies that took place in Denmark and Sweden, did not find an important difference in the danger for ASD from *In vitro* fertilization. However, they found a high risk in some subgroups, such as girls and children resulting from certain IVF procedures. Another study found no relation the evaluated prevalence of ASD and multiple births between U.S. births in 1994, in contrast to the detection of increased rates of autism between multiple births [3].

Discussion

From 1978 until 2010, almost 5 million babies were born with (IVF) methods. However, not enough data is available on the neuro-development of infants after *In vitro* fertilization, particularly for children over 1 year old. The association between the use of (ART) and (ASD) has been investigated in several studies. However, the results are still unfounded, although it appeared that ART use might be associated with a higher risk for ASD in some cases. Multiple births were found to play an essential role in the relationship between ART and autism. Actually, the calculated danger of ART was not notably increased among singletons. An immediate but not certain result of the Assisted Reproductive Technology methods. is the higher order double and multiple births Premature and young births, diabetes, hypertension, and caesarean section also appear to be mediators of the ART-autism relationship. Nevertheless, this phenomenon could be incidental, creating dangerous pregnancies that, without ART, would have never occurred. The procedures supporting this link need further investigation.

Conclusions

Generally, the majority of the research shows that ART is less dangerous to couples whose pregnancies were already at higher risk for ASD, like male infants and elderly parents. There are many possible methods by which Assisted Reproductive Technology may be related to ASD, including biological factors related to fertility or the quality of the germ cell, the effects of fertility hormones used in ART, and perinatal complications related to ART method.

Overall, all studies indicate the importance of further research into large population data sets. Because of the constantly growing use of Assisted Reproductive Technology, and the growing prevalence I and undetermined cause of ASD, it is essential to further investigate if those incidents are related.

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Volume 13 Issue 3 March 2022

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