Review Article

Assisted reproductive technology and its Association with autism in children

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Abstract

The use of assisted reproductive technology for conception has slowly increased over time. There has been a concern about the risk of autism spectrum disorders in children conceived. The relationship between assisted reproductive technology and autism spectrum disorders is complex and results are conflicting. More robust studies are needed to arrive at a definitive conclusion.

Keywords: autism spectrum disorders, assisted reproductive technology, infertility

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INTRODUCTION

Louise Joy Brown, the world's first baby conceived via in vitro fertilization (IVF), was born in 1978. Since then, many advances have been made in the field of assisted reproductive technology (ART).

Globally, over 5 million children have been conceived using ART.[1] In the United States, about 1.8% of all infants born are conceived with ART.[2] And the numbers are still increasing worldwide. Therefore, it is important to evaluate the safety of these ART procedures in relation to the long-term effect on children conceived via them. One area of research is the potential association between ART fertility treatments and autism.

AUTISM

Autism spectrum disorders (ASD) are neurodevelopmental conditions characterized by impaired social interaction and communication, together with restricted and repetitive behavior (American Psychiatric Association, 2000).[3] The National Survey of Children's Health (NSCH) 2016 and the National Health Interview Survey (NHIS) 2015–2017 both estimated ASD prevalence at 25 per 1000 children aged 3 to 17 years.[4,5] The Autism and Developmental Disabilities Monitoring (ADDM) Network observed that the combined ASD prevalence, in the United States at 11 sites, was 18.5 per 1000 (1 in 54) children aged 8 years.[6] Broadening of diagnostic criteria as well as early recognition of ASD due to increased awareness may have accounted for this increase in prevalence.

In India, there is a scarcity of high-quality population-based epidemiological studies on ASD. A systematic review done by Chauhan *et al.*[7] showed a pooled percentage prevalence of 0.11 [95% confidence interval (CI) 0.01–0.20] of ASD in children aged 1 to 18 years from the rural setting; and a pooled percentage prevalence of

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0.09 (95% CI 0.02–0.16) of ASD in children aged 0 to 15 years from the urban setting.

ASD not only affects the child and the family but also has direct and indirect cost implications on the nation. Resources have to be utilized to provide health care, targeted supportive education, and rehabilitative services to these children.

ETIOLOGY

The etiology of autism spectrum disorders is multifactorial and unknown at times. It is influenced by genetic and environmental factors that affect the developing brain. A strong genetic origin of ASD has been suggested by Bailey et al.[8] The phenotypic expression of this genetic factor is variable and is influenced by a number of environmental factors.[9] Advanced parental age, maternal disease, prenatal, perinatal, and postnatal environmental factors can influence ASD.[10,11] Among the environmental factors, the use of ART, including ovulation induction, IVF, and intracytoplasmic sperm injection (ICSI) have been suggested as a potential influencing factor. A higher risk of ASD in children born after ART may also be due to the higher rates of multiple births, preterm birth[12] and low birth weight deliveries[13] seen in these patients.

ASSOCIATION

The findings of relationships between infertility, infertility therapies, and autism spectrum disorders have been conflicting and inconsistent. Positive association of ART with autism was found in a few studies. In a large retrospective cohort study done in California,[14] the authors observed that the incidence of diagnosed autism was twice high for ART births compared to non-ART births. The association was decreased by excluding mothers unlikely to use ART; adjustment for demographic and adverse prenatal and perinatal outcomes reduced the association substantially, although statistical significance persisted for mothers aged 20 to 34 years. The authors concluded that the association between ART and autism is primarily explained by adverse prenatal and perinatal outcomes and multiple births. In India, a case-control study[15] was done that found that the hormonal interventions were higher among mothers who had children with ASD than the control population. Of the ASD cases analyzed, 58 mothers had undergone hormonal interventions (12.3%), whereas there were only 22 mothers among controls who underwent hormonal interventions (4.6%). They concluded that maternal hormonal intervention [odds ratio (OR) = 2.24] was a significant risk factor for ASD.

A large meta-analysis[16] was done to quantitatively evaluate the association between the use of ART and the risk of ASD in offspring. In this meta-analysis, 8,161,225 patients were included. The authors found a significant association between ART and the risk of ASD in especially in European and Asian populations. They concluded that ART may be an independent risk factor for ASD in offspring.

Few other studies have found no such association of ART with autism. The CHARGE (CHildhood Autism Risk from Genetics and the Environment) population-based study compared the cases with ASD ($n = 513$) to controls ($n = 388$) with regards to the diagnoses and type of infertility and the infertility treatments given. It found no differences in infertility, infertility treatments, or hypothesized underlying pathways between cases and controls. The authors concluded that ART is not a strong independent risk factor for ASD.[17]

A study was carried out in Finland[18] to find the association between IVF and ASD. The authors observed that when only singletons pregnancies were included, there was an association between IVF and Asperger's syndrome in unadjusted analysis (OR: 2.0, 95% CI: 1.1–3.5) but this was not significant when adjusted for the mother's socioeconomic status or parity. On analyzing the boys and girls separately, they observed that there was a significant association between IVF and Asperger's syndrome for boys in an unadjusted analysis (OR: 2.1, 95% CI: 1.2–3.7) but this was not significant in the final adjusted model. This study showed no increased risk of ASD in children born after IVF.

Another study was done in Denmark[19] to assess the risk of autism spectrum disorders in children born (1995–2003) using ART compared with children born after natural conception. Of 33,139 (5.6%) children born from assisted conception, 225 (0.68%) had a diagnosis of ASD. Of the 555,828 children born after natural conception, 3394 (0.61%) had a diagnosis of ASD. In crude analyses, children born after assisted conception had an increased risk of a diagnosis of ASD: crude hazard rate ratio 1.25 (95% CI 1.09 to 1.43). After adjusting for maternal age, educational level, parity, smoking, birth weight, and multiplicity, this risk disappeared: adjusted hazard rate ratio 1.13. (95% CI 0.97–1.31). However, a subgroup analysis suggests possible associations in

women who received follicle-stimulating hormone indicating the need for further study.

Systematic reviews of seven observational studies were done by Conti *et al.*[20] to evaluate the risk of autism spectrum disorders in ART. Four out of seven studies, including the two with the best quality scores, did not show an association between ART and ASD. The two studies supporting an increased risk of autism following ART had the lowest quality scores, due to major methodological limitations. One study showed a protective role of ART. They concluded that there is no evidence that ART significantly increases the risk of ASD in the offspring.

Diop et al[21] studied the prevalence of autism spectrum disorders in Massachusetts by comparing children born via ART and children born to women with indicators of subfertility but no ART, to children born to fertile women. They said that compared to children born to fertile women, children born to ART, ICSI, or IVF, or subfertile women are not at increased risk of having ASD.

In a recent study, Jenabi *et al.*[22] studied the association between the use of ART and the risk of ASD among children. In the univariate analysis, there was a significant association among child sex, delivery mode, history of preterm delivery, history of using ART, maternal age at child's birth, and the risk of ASD. After the adjustment for other variables, this association was significant for male sex (2.66; 95% CI 1.11–4.31; $P = 0.001$) and history of using ART (4.03; 95% CI 1.76–9.21; $P = 0.001$). After the adjustment for confounder variables, they found no significant association between ART and the risk of ASD among children (4.98; 95% CI 0.91–27.30; $P = 0.065$). They concluded that after the adjustment for other variables, risk factors for ASD were male sex and history of preterm delivery.

An inverse association of ART to ASDs was found by Maimburg *et al.*[23] They observed that children born after assisted conception had a lower risk of developing infantile autism than their matched controls.

MULTIPLE BIRTHS

Few studies have suggested a strong association of ASD in twins.[14,24] Study done by Grether *et al.*[24] observed that among multiple births (21 cases, 54 controls), an increased risk of ASD was seen in women with history of infertility and when infertility evaluation and treatment was done around the time of index pregnancy conception; however, the sample size was small to arrive at a firm conclusion. A similar observation was made by Fountain *et al.*[14] for multiple births.

HORMONAL TREATMENT

A study was done in Israel to examine the effects of infertility treatments on the risk of ASD. Infertility treatments included IVF and five hormone treatments. Results showed that IVF treatment compared with spontaneous conception was not statistically significantly associated with the risk of ASD. Only progesterone hormone treatment was associated with a statistically significant ($P<0.05$) increased risk of ASD [relative risk (RR)=1.51, 95% CI 1.22–1.86] compared to the group with no progesterone treatment. They concluded that progesterone exposure during the critical period of fetal life elevated the risk of ASD, possibly reflecting epigenetic modification.[25]

Hormonal interventions involved in ovulation induction with or without intrauterine insemination have been related to ASD. Lyall *et al.*[26] studied the risk of ASD in women using fertility treatments. No significant associations were found by them. However, in subgroup analyses of women with maternal age $\geq$ 35 years ($n = 1020$), artificial insemination was significantly associated with ASD; ovulation induction was significantly associated with ASD in crude but not adjusted analyses (OR = 1.81, 95% CI 0.96–3.42). In particular, the study suggests women with advanced maternal age, independent of age itself, may be at moderately increased risk of ASD with certain fertility therapies such as ovulation drugs and artificial insemination.

Bay et al.[27] observed that there was a small increase in the incidence of mental disorders in children born after ovulation induction/intrauterine insemination.

INTRACYTOPLASMIC SPERM INJECTION

ICSI was originally developed for the treatment of male factor infertility.[28] The indication has expanded and now it is used in 67%[29] of all ART procedures regardless of infertility diagnosis.

Sandin *et al.*[30] carried out a study to examine the association between the use of any IVF and different IVF procedures and the risk of autistic disorder and mental retardation in the offspring in Sweden. They found that compared with spontaneous conception,

IVF treatment was not associated with the autistic disorder but was associated with a small but statistically significant increased risk of mental retardation. They also observed a statistically significant increased risk of autistic disorder following ICSI using surgically extracted sperm and fresh embryos (RR = 4.60) when compared with IVF without ICSI with fresh embryo transfer. The RR for mental retardation following ICSI using surgically extracted sperm and fresh embryos was 2.35 and following ICSI using ejaculated sperm and fresh embryos was 1.47. The risks associated with ICSI using frozen embryos were significant for mental retardation (RR = 2.36).

However, a study from Denmark found no effect of ICSI or conventional IVF on the neurodevelopment of children when compared with spontaneously conceived children.[27] In another study by Kissin et al.,[31] it was observed that the incidence of ASD was higher when ICSI was used compared with conventional IVF and lower when parents had unexplained infertility (among singletons) or tubal factor infertility (among multiples) compared with other types of infertility. It was seen that the associations with an autism diagnosis were stronger when ICSI was used without male factor infertility and with nonsurgical method of semen collection. Hence, suggesting that male factor infertility may not be the main risk factor for autism diagnosis in offspring. Possible explanations include the use of ICSI as a rescue technique when fertilization with conventional IVF fails among patients without male factor infertility.[32] This was contradictory to the study from Sweden[30] and needs further investigation.

In a systematic review, Catford *et al.*[33] compared the outcomes of ICSI-conceived offspring beyond the neonatal period to IVF-conceived offspring. They observed that the neurodevelopment in children conceived by ICSI and IVF were comparable. Growth and physical health were also similar. In another review,[34] they studied long-term health outcomes of ICSI-conceived offspring compared with spontaneously conceived offspring. They observed that the neurodevelopment of ICSI-conceived children seems comparable to spontaneously conceived children. No significant difference was seen in growth, vision, and hearing. However, important differences in reproductive, general physical, and metabolic health have been observed in fair quality studies.

The differences observed may be due to the treatment factors, the genetic origin of the children, or related to adverse obstetric outcomes associated with IVF treatment. Precise knowledge about the role of individual risk factors in assisted reproductive technology and ICSI procedure will help to modify the clinical practice to avoid potential harm. Until then, the procedure of ICSI should be used mainly for male-factor infertility.

CONCLUSION

The association between ART and autism still remains a matter of debate. Recent evidence do not show a significant increase in the risk of ASD in women using ART treatment. However, few studies including a meta-analysis suggest ART to be a likely independent risk factor for ASD in offspring. Further studies are needed to draw concrete conclusions.

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REFERENCES

1. Adamson GD, Tabangin M, Macaluso M, de Mouzon J. The number of babies born globally after treatment with the assisted reproductive technologies (ART). Fertil Steril 2013;100:S42.
2. Sunderam S, Kissin DM, Zhang Y, Folger SG, Boulet SL, Warner L, Callaghan WM, Barfield WD. Assisted reproductive technology surveillance—United States, 2016. MMWR Surveill Summ 2019;68:1.
3. American Psychiatric Association. Diagnostic Criteria from DSM-IV-TR. Washington, DC: American Psychiatric Association; 2000.
4. Zablotsky B, Black LI, Maenner MJ, *et al.* Prevalence and trends of developmental disabilities among children in the United States: 2009–2017. Pediatrics 2019;144:e20190811. doi: 10.1542/peds.2019-0811
5. Pediatrics 2019; 144:e20190811. CrossRefexternal icon PubMedexternal icon, US Department of Health and Human Services. Healthy people 2020. Washington, DC: US Department of Health and Human Services 2010.
6. Maenner MJ, Shaw KA, Baio J, *et al.* Prevalence of autism spectrum disorder among children aged 8 years — autism and developmental disabilities monitoring network, 11 sites, United States, 2016. MMWR Surveill Summ 2020;69:1-12.
7. Chauhan A, Sahu JK, Jaiswal N, *et al.* Prevalence of autism spectrum disorder in Indian children: a systematic review and meta-analysis. Neurol India 2019;67:100-4.
8. Bailey A, Le Couteur A, Gottesman I, *et al.* Autism as a strongly genetic disorder: evidence from a British twin study. Psychol Med 1995;25:63-77.
9. Veenstra-Vanderweele J, Christian SL, Cook EH Jr.. Autism as a paradigmatic complex genetic disorder. Annu Rev Genomics Hum Genet 2004;5:379-405.
10. Wang C, Geng H, Liu W, Zhang G. Prenatal, perinatal, and postnatal factors associated with autism: a meta-analysis. Medicine 2017;96: e6696.

11. Hodges H, Fealko C, Soares N. Autism spectrum disorder: definition, epidemiology, causes, and clinical evaluation. Transl Pediatr 2020;9 (suppl 1):S55.
12. Arpino C, Compagnone E, Montanaro ML, *et al.* Preterm birth and neurodevelopmental outcome: a review. Childs Nerv Syst 2010;26:1139-49.
13. Schendel D, Bhasin TK. Birth weight and gestational age characteristics of children with autism, including a comparison with other developmental disabilities. Pediatrics 2008;121:1155–64.
14. Fountain C, Zhang Y, Kissin DM, *et al.* Association between assisted reproductive technology conception and autism in California, 1997-2007. Am J Public Health 2015;105:963-71.
15. Mamidala MP, Polinedi A, Kumar PT, *et al.* Maternal hormonal interventions as a risk factor for Autism Spectrum Disorder: an epidemiological assessment from India. J Biosci 2013;38: 887-92.
16. Gao J, He X, Cai Y, Wang L, Fan X. Association between assisted reproductive technology and the risk of autism spectrum disorders in the offspring: a meta-analysis. Sci Rep 2017;7:46207.
17. Lyall K, Baker A, Hertz-Picciotto I, Walker CK. Infertility and its treatments in association with autism spectrum disorders: a review and results from the CHARGE study. Int J Environ Res Public Health 2013;10:3715-34.
18. Lehti V, Brown AS, Gissler M, Rihko M, Suominen A, Sourander A. Autism spectrum disorders in IVF children: a national case-control study in Finland. Hum Reprod 2013;28:812-8.
19. Hvidtjørn D, Grove J, Schendel D, *et al.* Risk of autism spectrum disorders in children born after assisted conception: a population-based follow-up study. J Epidemiol Community Health 2011;65:497-502.
20. Conti E, Mazzotti S, Calderoni S, Saviozzi I, Guzzetta A. Are children born after assisted reproductive technology at increased risk of autism spectrum disorders? A systematic review. Hum Reprod 2013;28: 3316-27.
21. Diop H, Cabral H, Gopal D, Cui X, Stern JE, Kotelchuck M. Early autism spectrum disorders in children born to fertile, subfertile, and ART-treated women. Matern Child Health J 2019;23:1489-99.
22. Jenabi E, Seyedi M, Hamzehei R, *et al.* Association between assisted reproductive technology and autism spectrum disorders in Iran: a case-control study. Clin Exp Pediatr 2020;63:368-72.
23. Maimburg RD, Vaeth M. Do children born after assisted conception have less risk of developing infantile autism? Hum Reprod 2007;22:1841-3.
24. Grether JK, Qian Y, Croughan MS, *et al.* Is infertility associated with childhood autism? J Autism Dev Disord 2013;43:663-72.
25. Davidovitch M, Chodick G, Shalev V, *et al.* Infertility treatments during pregnancy and the risk of autism spectrum disorder in the offspring. Prog Neuropsychopharmacol Biol Psychiatry 2018;86:175-79.
26. Lyall K, Pauls DL, Spiegelman D, Santangelo SL, Ascherio A. Fertility therapies, infertility and autism spectrum disorders in the Nurses' Health Study II. Paediatr Perinat Epidemiol 2012;26:361-72.
27. Bay B, Mortensen EL, Hvidtjørn D, Kesmodel US. Fertility treatment and risk of childhood and adolescent mental disorders: register based cohort study. BMJ 2013;347:f3978.
28. Palermo G, Joris H, Devroey P, Van Steirteghem AC. Pregnancies after intracytoplasmic injection of single spermatozoon into an oocyte. Lancet 1992;340:17-18.
29. Centers for Disease Control and Prevention, American Society for Reproductive Medicine, Society for Assisted Reproductive Technology. 2011 Assisted Reproductive Technology Fertility Clinic Success Rates Report. Atlanta: U.S. Department of Health and Human Services, 2013.
30. Sandin S, Nygren KG, Iliadou A, Hultman CM, Reichenberg A. Autism and mental retardation among offspring born after in vitro fertilization. JAMA 2013;310:75-84.
31. Kissin DM, Zhang Y, Boulet SL, *et al.* Association of assisted reproductive technology (ART) treatment and parental infertility diagnosis with autism in ART-conceived children. Hum Reprod 2015;30:454-65.
32. Beck-Fruchter R, Lavee M, Weiss A, Geslevich Y, Shalev E. Rescue intracytoplasmic sperm injection: a systematic review. Fertil Steril 2014;101:690-8.
33. Catford SR, McLachlan RI, O'Bryan MK, Halliday JL. Long-term follow-up of intra-cytoplasmic sperm injection-conceived offspring compared with in vitro fertilization-conceived offspring: a systematic review of health outcomes beyond the neonatal period. Andrology 2017;5:610-21.
34. Catford SR, McLachlan RI, O'Bryan MK, Halliday JL. Long-term follow-up of ICSI-conceived offspring compared with spontaneously conceived offspring: a systematic review of health outcomes beyond the neonatal period. Andrology 2018;6:635-53.