ORIGINAL ARTICLE: ASSISTED REPRODUCTION

No increase in autism-associated genetic events in children conceived by assisted reproduction

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Objective: To understand the rate of genetic events in patients with autism spectrum disorder (ASD) who were exposed to assisted reproduction.
Design: Case control study using genetics data.
Setting: Twelve collaborating data collection sites across North America as part of the Simons Simplex Collection.
Patient(s): 2,760 children with ASD, for whom 1,994 had published copy number variation data and 424 had published gene mutation status available.
Intervention(s): None.
Main Outcome Measure(s): Rates of autism-associated genetic events in children with ASD conceived with assisted reproduction versus those conceived naturally.
Result(s): No statistically significant differences in copy number variations or autism-associated gene-disrupting events were found when comparing ASD patients exposed to assisted reproduction with those not exposed to assisted reproduction.
Conclusion(s): This is the first large genetic association to concurrently examine the genotype of individuals with ASD in relation to their exposure to ART versus natural conception, and it adds reassuring evidence to the argument that ART does not increase the risk of ASD. (Fertil Steril® 2014;■:■–■. ©2014 by American Society for Reproductive Medicine.)
Key Words: Assisted reproduction, assisted reproductive technology, autism, copy number variation

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Autism spectrum disorder (ASD) is a neuropsychiatric condition that includes impairments in social interaction and communication as well as restricted or stereotyped behavior (1). The prevalence of ASD in U.S. children aged 6 to 17 years is estimated to be as high as 1 in 50 from recent data (2). The etiology of ASD is unknown; however, there is strong evidence of significant genetic influence, with hundreds of genes implicated, each of which generally conveys a slight increase in risk (3, 4). Autism risk is also elevated after environmental insult including in utero exposure to infections, toxins, and birth complications among others (5–7). More recently, epigenetic factors have been proposed as playing a significant role in the etiology of ASD, highlighting the contribution of both genetic and environmental factors (8, 9). Given the building evidence for the interplay of genetics and environment in the etiology of ASD, it is important to consider whether certain medical interventions may also play a role.

Assisted reproduction is a broad term referring to various interventions primarily used to treat infertility, including but not limited to fertility medications, in vitro fertilization (IVF), gamete intrafallopian transfer (GIFT), zygote intrafallopian transfer (ZIFT), and artificial insemination. Assisted reproductive technology (ART) as defined by the Centers for Disease Control and Prevention, is a more specific term, only including IVF, GIFT, and ZIFT. These three treatments alone

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accounted for 163,038 ART cycles resulting in 47,090 live births in 2011 (10).

As ART has become increasingly common, there have been concomitant concerns regarding the developmental outcomes of these pregnancies. Fortunately, major reviews and individual studies of ART procedures have been overall reassuring (11, 12). In general, neurodevelopmental outcomes of children conceived by ART seem to be comparable to outcomes in spontaneously conceived children (13). A number of studies have demonstrated that neither intracytoplasmic sperm injection (ICSI) or IVF are associated with cognitive disorders, developmental delays, or psychological/behavioral issues (14–21). Other studies have disputed the possibility of an association between IVF and a higher rate of karyotype abnormalities (22, 23).

Despite the positive outlook from these broad outcome measures, a number of specific differences have been observed between the outcomes of pregnancies conceived spontaneously versus those with ART. There have been suggestions that ART may affect genetic events that occur during ovulation or fertilization, such as with imprinted genes. Of the nine known imprinting syndromes, ART has been associated with two: Beckwith-Wiedemann syndrome and Silver-Russell syndrome (24). Moreover, it has been reported that the total risk of congenital malformations may be increased by about one-third through ART, with approximately a twofold increased risk of nervous systems defects (25). Pregnancies from IVF are also at higher risk for low birth weight and preterm birth compared with pregnancies conceived spontaneously (26–28). There are also other differences between IVF pregnancies and spontaneously conceived pregnancies, the most well known of which has been the increased multiple gestation rates (29). Specifically in regards to ICSI, there has been some recent evidence that ICSI is associated with mental retardation (30).

Various studies, primarily epidemiologic, have looked at the association between ASD and ART (30–35). Overall, the available data have not found a clear association between ASD and ART, but the results have not been entirely uniform. A 2009 meta-analysis looked at eight studies that examined possible relations between ART and ASD (35). The investigators noted methodological problems in the available studies as well as inconsistent results, and concluded that "possible associations with ASD need assessment in larger studies." One recently published study concluded that ART was a risk factor for ASD (33), but another study claimed the opposite (34). However, the investigators in the latter study noted that the apparent increase in risk was due to confounding factors such as maternal age, educational level, parity, smoking, birth weight, and multiplicity. Another recent epidemiologic study documented similar findings, concluding that the risk between ASD and IVF disappeared once the analyses had been adjusted (31). It may be particularly important to adjust for parental characteristics because users of ART are more likely than fertile individuals both to be of increased age and to have chromosomal abnormalities (20). Furthermore, recent studies have shown that older paternal age is associated with autism-associated de novo copy number variation (CNV) (36, 37).

Perhaps most notably, a recent systematic review of many of the observational studies regarding ASD and ART concluded that there is no evidence that ART is significantly associated with ASD (38). Importantly, it should be pointed out that the findings tying ART to imprinting disorders seem particularly relevant in the context of ASD because imprinting disorders involve aberrant methylation (an epigenetic change in the quantity of methyl groups attached at certain sites in the genome) and aberrant methylation has been implicated in ASD (39). Finally, although there has been specific attention to ASD and ART, the broader question of whether assisted reproduction in general is associated with ASD has also been raised (32).

Although these studies have proven informative, no study to date has concurrently examined the genotype of individuals with ASD in relation to their exposure to ART versus natural conception. Given the concerns regarding the effect of ART on pregnancy outcomes, including genetic abnormalities, and in the context of the identified genetic contributions to ASD risk, it is important to look more specifically at the autism-associated genetic anomalies in ASD patients exposed to assisted reproduction. Therefore, we examined the relation between assisted reproduction and genetic mutations in children with ASD.

MATERIALS AND METHODS

Participants were 2,760 4- to 18-year-old children with ASD and their families who previously had participated in the Simons Simplex Collection (SSC). The SSC, a project funded by the Simons Foundation Autism Research Initiative to identify de novo genetic variants related to ASD, includes 12 collaborating data collection sites across North America (for a description of the ascertainment, data collection, and validation procedures for the sample, see http://sfari.org) (40). Approval was obtained from each local institutional review board. All participants completed informed consent before participation in the study. As part of SSC study participation, experienced clinicians confirmed the ASD diagnosis using the Autism Diagnostic Interview, Autism Diagnostic Observation Schedule, and expert clinical judgment according to Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV) criteria (41).

Information regarding assisted reproduction was collected through a clinician-administered, semistructured caregiver interview designed to gather data regarding early medical history for children and families participating in the SSC. Clinicians administering the interview were primarily specialists in mental health, not obstetrics. Specific to this study, caregivers were asked whether assisted reproduction had been used to initiate the pregnancy of the proband or siblings. If the caregiver responded yes, data regarding what type of assisted reproduction was collected. The options were oral fertility medications, injected fertility medications, artificial insemination, IVF, assisted hatching, frozen embryo, frozen eggs, sperm donor, egg donor, ICSI, GIFT, ZIFT, surrogacy, unknown, and other. Additionally, the maternal and paternal age at the time of conception was gathered.