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## Parent-reported use of assisted reproduction technology, infertility, and incidence of autism spectrum disorders

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## ABSTRACT

In this study, we explored the relationship between the rise in the incidence of autism spectrum disorder (ASD), the rise in the use of assisted reproductive technology (ART), and the role of infertility. We compared the incidence of ASD in children conceived with and without the use of ART. We also considered the incidence of ASD in children whose parents reported issues of infertility. Ninety families completed a confidential questionnaire and reported use of ART, ASD diagnoses of their children, infertility, parent age at time of conception, socioeconomic status, and other variables. We obtained information for a total of 163 children. Findings indicate that there is not a significant difference in the incidence of ASD diagnoses among participants who used ART compared to those that did not. Additionally, infertility was not found to be associated with increased rates of ASD diagnoses. Limitations include small sample sizes and reliance on parent report. Implications are discussed.

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### 1. Introduction

Current estimates by the Center for Disease Control (CDC) indicate that one in 68 children are diagnosed with autism spectrum disorder (ASD). This is a significant increase from the published figures from 2000 that reported one in 150 children was diagnosed with ASD. Recently there has been a proliferation of studies that seek to determine the cause(s) of the disorder. Many have found genetic mutations associated with ASD (e.g., Giza et al., 2010; Miles, 2011) and others suggest high heritability of the disorder (Hallmayer et al., 2011). Other risk factors implicated in the manifestation of ASD include parental age, socioeconomic status, infertility (e.g., Davies et al., 2012; Leslie, 2004; Shimada et al., 2012) and shortened gestation (Leavy et al., 2013; Schieve et al., 2014). At present, a single cause has not been identified. Researchers studying ASD epidemiology overwhelmingly agree that there is likely not a single cause but rather a combination of factors that cause the disorder, and the combination is likely related to gene-environment interactions. However, research that considers combinations of variables across populations is limited, and findings vary widely among studies.

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In addition to the increase in the incidence of ASD, the incidence of live births as a result of the use of assisted reproduction technology (ART) is also on the rise. Based on the 1992 Fertility Clinic Success Rate and Certification Act, the CDC (2012) defines ART as any fertility measure taken that manipulates both the egg and the sperm. Typical ART procedures include removal of eggs from the ovaries, collection of sperm, laboratory combination, and either reinsertion or donation to another carrier. These include in vitro fertilization (IVF) and intracytoplasmic sperm injection (ICSI). By this definition, procedures that manipulate the sperm only (e.g., intrauterine insemination) or medications taken to stimulate egg production (without the intention of egg retrieval) do not qualify as ART. ART procedures that do fall under this definition have the potential to affect the genetic structure of the genome, fertilized eggs and embryo (Lu, Wang, & Jin, 2013; Shimada et al., 2012) and some studies have found that their use, particularly ICSI, may result in chromosomal abnormalities (Bonduelle et al., 2002).

Known risk factors of ART use include preterm labor, low birth weight, multiple births, birth defects, and adverse psychological outcomes (Beydoun et al., 2010; Klemetti, Sevón, Gissler, & Hemminki, 2006). The use of ART has recently been introduced as a possible associated risk factor of ASD. Of note is that ART use appears to have a higher rate of use among certain populations that may already have an elevated risk of having a child diagnosed with ASD, such as those with increased maternal and paternal age at the time of conception (Sandin et al., 2012; Shimada et al., 2012) those with mental health issues (Klemetti, Raitanen, Sihvo, Saarni, & Koponen, 2010), and fertility problems (Davies et al., 2012; Grether et al., 2013; Lyall, Pauls, Spiegelman, Santangelo, & Ascherio, 2012; Zhu, Basso, Obel, Bille, & Olsen, 2006).

Despite these risks, there has been a steady and significant increase in the number of clinics that provide ART services and the number of infants born as a result of ART use. In 2012, the CDC reported that the use of ART has doubled in the past decade and estimated that over 1% of all children born in the US were conceived through ART. According to CDC's ART Fertility Clinic Success Rates Reports, 64,681 cycles were performed in 1996 (14,501 live births; 20,840 infants). That number increased to 134,260 cycles in 2005 (38,910 live births; 52,041 infants). In 2011, 163,038 ART cycles were performed, resulting in almost 48,000 live births (61,610 infants).

### 1.1. Risks of ART use

The incidence of birth defects in children conceived via certain types of ART (ART+) is higher than that noted in the rest of the population (e.g., CDC, 2009; Davies et al., 2012). Compared to children conceived without the use of ART (ART–), the CDC (2011) reports a higher risk of pre-term delivery and of low and very low birth weight (c.f. Zachor & Itzchak, 2011) and an increased probability of multiple-fetus pregnancy associated with various types of ART use (Lu et al., 2013). Even singleton infants conceived via ART are reported to be at a higher risk for adverse perinatal outcomes, compared to infants conceived without the use of ART (Davies et al., 2012; Knoester et al., 2008). Additionally, the women who used any type of assisted conception in Davies et al.'s (2012) study had a higher rate of incidence of stillbirth, delivery by cesarean section and delivery at less than 37 weeks. Mothers who conceived using ART were less likely to have a male singleton and their children had lower birth weights than children of mothers who did not conceive using ART. These risks seem to increase with particular causes of infertility (Davies et al., 2012), and increased maternal (Sandin et al., 2012) and paternal age (e.g., Parner et al., 2011; Shimada et al., 2012; Smith et al., 2014).

The National ART Surveillance System (NASS), the only CDC-approved ART monitoring system, reports patient demographics, obstetrical and medical history, parental infertility diagnosis, clinical parameters of the ART procedure, and information on resultant pregnancies. NASS, however, does not report on long-term outcomes or health status of children born as a result of ART use. Long-term developmental and psychological outcomes of children conceived via ART have been of interest to researchers since ART's early use. Of the first cohort to be conceived through ART, many later reported various psychological health problems (Beydoun et al., 2010). Studies of older children and adolescents conceived via ART also reported various psychological health problems, disorders of behavioral and emotional development (Klemetti et al., 2006), and externalizing and more withdrawn and depressed behaviors (cf. Knoester et al., 2008; Wagenaar, Huisman, Cohen-Kettenis, & Delemarre-van de Waal, 2008), and cognitive delays (Ponjaert-Kristoffersen et al., 2005; Sandin, Nygren, Iliadou, Hultman, & Reichenberg, 2013). However, no differences of mental and psychomotor abilities were found in comparing 2 year-olds who were conceived using ICSI and without the use of ART (Nekkebroeck, Bonduelle, Desmyttere, Van den Broeck, & Ponjaert-Kristoffersen, 2008). These conflicting results indicate the need for longer follow-up for children conceived using ART.

Several studies have examined the prevalence of ASD in children conceived via ART. The preliminary evidence suggests that the prevalence of ASD is higher in children conceived via ART than those who were conceived without assistance (see Knoester, Helmerhorst, van der Westerlaken, Walther, & Veen, 2007). Shimada et al. (2012) conducted a chart review of people in Japan diagnosed with ASD, attention deficit hyperactivity disorder (ADHD), and Tourette's syndrome. Results indicated that ART use among parents of children with ASD was 1.8 times higher than that of the general population. However, no significant difference in rate of ART use was found for parents of children with ADHD and Tourette's compared to the general population. ART use among parents of children with ASD in Israel has also been reported to be significantly higher than that of the general populations (Zachor & Itzchak, 2011).

### 1.2. Pilot study

In order to examine whether there is an increased risk of having a child diagnosed with ASD or other communication disorder (CD) with use of ART, the authors conducted a pilot study. Parents of children conceived using ART (ART+,  $n = 13$ )

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