

Does ICSI really increase autism risks?

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Autism is a serious neurodegenerative condition with largely unknown etiologies. According to the CDC, the prevalence of autism in the United States appears to have rapidly risen from about 6.7 per 1,000 in 2002 to 14.7 per 1,000 in 2010 (3). Caucasian children, according to the same CDC report, however, are 30% more likely to be diagnosed with autism than children of African descent (2012).

Rather than due to racial or ethnic differences, this discrepancy has been attributed to varying diagnostic practices in different socioeconomic settings. (Durkin, et al., 2010, Hoffman, et al., 2012, Pedersen, et al., 2012, Zuckerman, et al., 2013). It seems likely that the same socioeconomic factors biasing the diagnosis of autism, also affect which patients utilize assisted reproductive technologies (Bitler and Schmidt, 2006, Chandra and Stephen, 2010, Duwe, et al., 2010, Jain, 2006). Since ICSI adds significant expense to an already expensive procedure, one can surmise that socio-economically advantaged patients would utilize ICSI to a higher degree, especially during the years covered in the CDC study, when ICSI was still an emerging technology (Palermo, et al., 1995).

Kissin et al, recently reported that intracytoplasmic sperm injection (ICSI) was associated with increased risk of autism (Kissin, et al., 2015). Kissin et al. did not adjust their data analysis for race/ethnicity and/or socioeconomic status, while their statistical models were adjusted for infant gender, gestational age, birth weight, multiple pregnancy, birth year, parental age at delivery, number of previous births, mode of delivery, and fertility diagnosis.

We have to acknowledge that direct indicators of socioeconomic status are not available on birth certificates; but birth certificate information to reconstruct socioeconomic status has been utilized by other investigators in similar epidemiologic studies (Moceri, et al., 2001). It is, therefore, rather striking that the manuscript does not even make reference to or acknowledges this very obvious and important possible confounder to their analysis.

Kissin et al. noted that ART cycles associated with ICSI increased from 33% in 1996 to 60% in 2006 (an 81.82% increase), and that during the same time period the incidence of autism among ART patients remained steady around 1%, with an expected higher incidence among multiple pregnancies compared to singleton pregnancies (1). If ICSI, indeed, increased the risk of autism by almost 82%, it stands to reason that, commensurate with this increased proportion of ICSI cycles, there should have been a concomitant increase in autism among ART patients. Such an increase was, however not observed.

Recognizing this fact as a potential contradiction, the investigators suggested that absence of such an observed increase in autism among all ART patients might have been the consequence of decreasing multiple gestations due to fewer embryos being transferred. However, multiple pregnancies was a factor the authors, indeed, adjusted for in their analysis (Kissin, Zhang, Boulet, Fountain, Bearman, Schieve, Yeargin-Allsopp and Jamieson, 2015).

This study's conclusion that the utilization of ICSI in California between 1997 and 2006 was associated with an increased adjusted hazard risk for autism, therefore, appears incorrect.

Translational relevance: This presentation reminds us of the importance to identify and properly analyze potential confounding factors in epidemiological studies. Such adjustments become even more important as large registries give rise to very large data sets in which even small clinical differences can achieve statistical significance.