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Reply: CDC analysis of ICSI/autism: association is not causation

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Sir,

We appreciate the interest of Dr Barad *et al.* in our analysis of the association of assisted reproductive technology (ART) treatment and parental infertility diagnosis with autism in ART-conceived children (Kissin *et al.*, 2015).

Dr Barad *et al.* express concern that the analysis was not adjusted 'for race/ethnicity and/or socioeconomic status.' We did consider both maternal race/ethnicity and education (the latter as a proxy for socioeconomic status) among other characteristics for inclusion in models that explored the association of autism with ART treatment factors and parental infertility diagnosis. Neither factor was significant in the univariable analysis and, therefore, was not included in in the models. However, in response to Dr Barad *et al.*'s suggestion, we refit the models with addition of these two factors. As expected, the risk estimates for the association of ICSI with autism diagnosis remained statistically significant for both singletons [adjusted hazard risk ratio, aHRR 1.73 (1.11–2.69)] and multiples [aHRR 1.51 (1.06–2.15)].

Contrary to Dr Barad *et al.*'s surmise that socioeconomically advantaged patients would utilize ICSI to a higher degree, there was no evidence that utilization of ICSI was significantly associated with either race/ethnicity (70% of ART users with ICSI were non-Hispanic white, compared with 70% of ART users without ICSI) or socioeconomic status (89% of ICSI users were college graduates, compared with 87% of women who used ART without ICSI).

The dramatic increase in use of ICSI during the study period without similar increase in autism diagnosis in ART-conceived children can likely be explained by the relatively low prevalence of autism. Using a mathematical assessment model for estimating the effects of

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changes in the prevalence of individual risk factors on autism prevalence (Schieve *et al.*, 2011), we estimate that the 82% increase of ICSI use would be expected to result in a 14.4% increase in autism among singletons, and thus a prevalence increase from0.9 to 1.03%. Likewise, the ICSI use increase we observed would be expected to result in a 15.5% autism increase among multiples, which translates to a prevalence increase from 1.2 to 1.39% among multiples. Such small increases in autism prevalence are difficult to detect with any precision. Moreover, while increasing ICSI utilization may have led to a slight increase in autism prevalence, other factors, such as the decline in multiple births among ART deliveries, might have affected the trend in the opposite direction.

As we clearly noted in our article, an underlying biological mechanism through which ICSI could be associated with autism is not known and may be related to the procedure itself, characteristics of the patients selected for the procedure, or other factors. However the possibility of risk and the lack of convincing evidence of benefit do not appear to favor use of ICSI without male-factor infertility diagnosis (ASRM, 2012).

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