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LETTER TO THE EDITOR

Cerebral palsy in children born after assisted reproductive technology; is there a true association?

Sir,

We read the article by Carlsen et al. entitled "Cerebral Palsy in children born after assisted reproductive technology in Norway: Risk, prevalence and clinical characteristics",[1] and we commend the authors for addressing a vital concern. Nevertheless, we would like to express several concerns with their analysis and conclusions.

As presented, several studies suggest an increase in the risk of a child born with cerebral palsy (CP) following assisted reproductive technology (ART), including findings from the Danish National Birth Cohort.[2] Preterm birth is a known risk factor for CP, and the authors found an adjusted odds ratio (OR) of 1.32 (95% CI 1.02–1.71) in the ART group compared with natural conception. Additional multivariate logistic regression analyses would be helpful to assess whether the higher prevalence of CP was related to the higher prevalence of preterm birth and low birthweight among ART children and to include further adjustments for gestational age, multiplicity and birthweight.

From 2002 to 2015, the study demonstrated a decline in the overall prevalence of CP with an intervening period from 2008 to 2012 (figure 2 in Carlsen et al.[1]) consistent with the worldwide results.[3] The authors neglected to stratify data based on outcomes of the prenatal, perinatal and postnatal periods, which are metrics that are considered to be potential contributors to the development of CP.[4] Other key limitations are the lack of analysis regarding the mode/indication of delivery (cesarean vs instrumental delivery) with any acute hypoxic events, and determining the number of embryos transferred, which could increase the risk of a multiple gestation and/or a vanishing twin and could increase the risk of CP from prematurity.

The authors state: "After restriction to multiples, children born at term after ART had nearly 50% higher odds of CP than children born at term after natural conception". However, the results were not significant by a crude or adjusted odds ratio. Upon further dividing into singletons and multiples, the adjusted ORs were not significant compared with natural conception (table I in Carlsen et al.[1]). Consequently, we disagree with the study's "Key Message" of an increased risk of CP associated with ART "mainly attributed to multiple pregnancies", as the data do not support a statistically significant relationship.

The unexplained decline in CP prevalence from 2002 to 2015, observed in both groups, contributes to the difficulty interpreting the results, particularly since the ART group demonstrated a steeper drop with an even lower prevalence in 2007 and 2011 (figure 2 in Carlsen et al.[1]) compared with natural conception.

A proposed area for further investigation would include determining the incidence of CP in children born after ovulation induction with intrauterine insemination vs natural pregnancy following a diagnosis of infertility in order to potentially postulate the contribution of infertility as an independent risk factor for the development of CP.

Infertility is a devastating disease that contributes to anxiety and depression scores equivalent to other major medical morbidities, including cancer and cardiovascular disease.[5] We applaud the authors for addressing a potential concerning association, yet would put in a plea for accurate interpretation of results to avoid sensationalism and the consequential unnecessary alarm to emotionally impacted infertility patients.

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