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LETTER TO THE EDITOR

The increased risk of cerebral palsy associated with assisted reproductive technology is mainly attributable to multiple pregnancies

Sir,

We thank Dr Jayakumaran and colleagues[1] for their interest in our study.[2] It is our understanding that their main concerns are the need for additional analyses, and a disagreement with our key message "There is still an increased risk of cerebral palsy associated with assisted reproductive technology (ART), mainly attributable to multiple pregnancies." We appreciate that they expressed this concern.

This has encouraged us to perform additional analyses, that is, mediation analyses, to investigate the causal pathway from ART to cerebral palsy (CP). Figure S1 in our original publication illustrates three potential mediation pathways[2]:

ART ➔ multiple pregnancy ➔ CP
ART ➔ gestational age ➔ CP
ART ➔ multiple pregnancy ➔ gestational age

We have analyzed these three pathways using the "mediate" command, a new feature in Stata 18. The mediators, multiple pregnancies (twins and above) were categorized as multiples vs singletons, and gestational age as preterm (<37 weeks) vs term (≥37 weeks). The mediators and the outcome variables were dichotomous, and these were modeled using the logit link function, corresponding to logistic regression. A treatment-mediator interaction was included in the analyses. We also included the following potential confounders between ART, the mediator, and the outcome, as illustrated in Figure S1 in our original publication[2]: parity, mother's health before pregnancy, and mother's age.[2] We report the results on a risk difference scale (Table 1).

Table 1A shows the results for multiple pregnancy as a potential mediator of the effect of ART on CP. The estimated risk for CP if no ART was used is 0.00192. This is denoted as T0 M0, meaning no treatment (T0), and the risk of multiple pregnancy given no treatment (M0). Similarly, the estimated risk of CP given ART is 0.00382 (denoted as T1 M1). Thus, the estimated total effect of ART on CP is the risk difference, which is 0.00189 (equal to 0.00382–0.00192). Now, consider a potential outcome if ART is given, but the risk for multiple pregnancy is kept at what it would be if no treatment were given. This is denoted T1 M0, and the corresponding estimated risk is 0.00252. Thus, the estimated natural indirect effect of ART on CP mediated through multiple pregnancy is the risk difference 0.00130 (equal to 0.00382–0.00252). Moreover, the estimated natural direct effect, not mediated through multiple pregnancy is 0.0059 (equal to 0.00252–0.00192).

Hence, on a risk difference scale, an estimated proportion of 69% (0.00130/0.00189) of the effect of ART on CP is mediated through multiple pregnancy.

What is the role of gestational age in this context? Table 1B shows the results for preterm birth as a potential mediator of the effect of ART on CP. The results are similar to that for multiple pregnancies: a substantial proportion 75% (0.00146/0.00194) seems to be mediated through preterm birth.

In Table 1C, we also found that the effect of ART on preterm birth is mainly mediated through multiple pregnancies, which mediates an estimated proportion of 76% (0.0806/0.1056).

Hence, we see that the mediation through preterm birth is mainly due to the causal pathway through multiple pregnancies.

In order to make a causal interpretation of a mediation analysis, we must assume that there are no unmeasured confounders for the relationships between treatment, mediator or outcome.[3] In the present analyses, we have included parity, mother's health before pregnancy, and mother's age as confounders. We regard these to be potentially strong confounders and consider it unlikely that there are other unmeasured confounders of such strength.

Our original interpretation was based upon the observed very high (32%) prevalence of multiple pregnancies and preterm births (18%) among children born after ART compared to after natural conception (2.9% and 6.3%, respectively), as well as on the finding (CP-subtypes and impairments) suggesting that among children born after ART the pathophysiological mechanisms leading to brain injury and CP are similar in children born after natural conception.[2] The subgroup analyses referred to by Dr Jayakumaran and colleagues were not included in this interpretation.

TABLE 1 Results of mediation analyses to investigate the causal pathway from assisted reproductive technology (ART) to cerebral palsy (CP).

	Coefficient		
	Estimate	**95% confidence interval**	***p*-value**
A. Mediation analysis ART ➔ multiple pregnancy ➔ CP			
Potential outcome mean			
T0M0	0.00192	0.00183–0.00202	<0.001
T1M0	0.00252	0.00184–0.00320	<0.001
T1M1	0.00382	0.00304–0.00459	<0.001
Natural indirect effect	0.00130	0.00080–0.00179	<0.001
Natural direct effect	0.00059	−0.00009–0.00128	0.091
Total effect	0.00189	0.00111–0.00267	<0.001
B. Mediation analysis ART ➔ preterm birth ➔ CP			
Potential outcome mean			
T0M0	0.00192	0.00182–0.00202	<0.001
T1M0	0.00240	0.00183–0.00297	<0.001
T1M1	0.00386	0.00307–0.00464	<0.001
Natural indirect effect	0.00146	0.00105–0.00186	<0.001
Natural direct effect	0.00048	−0.00010–0.00105	0.10
Total effect	0.00194	0.00115–0.00273	<0.001
C. Mediation analysis ART ➔ multiple pregnancy ➔ preterm birth			
Potential outcome mean			
T0M0	0.0629	0.0623–0.0634	<0.001
T1M0	0.0879	0.0842–0.0917	<0.001
T1M1	0.1686	0.1638–0.1733	<0.001
Natural indirect effect	0.0806	0.0771–0.0841	<0.001
Natural direct effect	0.0250	0.0212–0.0288	<0.001
Total effect	0.1056	0.1009–0.1104	<0.001

The results of the mediation analyses corroborate our interpretation and the key message.

Furthermore, in our publication, we found a substantial decrease in the prevalence of CP after ART from 2002 to 2015, as shown in Figure 2 in our original publication.[2] The decrease in CP coincides with the decreasing use of more than one embryo in ART during this time.

Regarding the decline in the prevalence of CP among children born after ART, Dr Jayakumaran and colleagues propose 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.*"[1] However, in our context, we regard these metrics to be potential colliders, that is, effects of the treatment, mediator or outcome. Adjusting for colliders will generally introduce bias.

Lastly, we agree with Dr Jayakumaran et al.'s "*…plea for accurate interpretation of results to avoid sensationalism and the consequential unnecessary alarm to emotionally impacted infertility patients.*"[1] However, we thought that the findings from our original study[2] would be appreciated as reassuring both by parents and professionals as the results suggest a low absolute risk and a decreasing prevalence of CP, despite increased use of ART.

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