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Commentary: Context matters for the postnatal sequelae of being born low birthweight

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As the proportion of children being born as a result of medically assisted reproductive (MAR) technologies increases rapidly across the globe, epidemiologists are increasingly interested in understanding how these complex and evolving interventions that have provided welcome solutions to subfertility for so many parents also contribute to offspring wellbeing beyond the perinatal period.

In some European countries, births after MAR now represent ~10% of all births, so understanding the impact of MAR on life-course wellbeing outcomes is not trivial.[1]

Understanding the impact that MAR has on childhood cognition is especially important because of the associations with whole-of-life-course wellbeing and productivity.[2]

Children born after MAR are known to have a greater chance of experiencing poorer perinatal outcomes, including being born with a low birthweight (LBW) compared with naturally conceived births. In naturally conceived births, LBW usually predisposes offspring to relative cognitive disadvantage.[3]

However, after MAR, children are not generally disadvantaged cognitively compared with their naturally conceived peers according to a recent systematic review.[4] The review also highlighted that only a handful of the hundreds of studies that investigated this association were ranked as being of high quality. Common limitations of studies included the lack of large and detailed life-course data sets used and selection bias in the populations included, with a bias towards the exclusion of children at greatest risk of cognitive impairment.[4]

Evaluating postnatal outcomes for offspring born after MAR is particularly challenging because the underlying reasons for parental subfertility and the need for MAR are also poorly understood. Additionally access to MAR is not equitably distributed according to need. Parents who are able to access MAR, especially in the UK, tend to be more socio-economically advantaged than the general reproductive population .

Cozzani *et al.* begin to address some of these challenges in their recent paper.[5] They extend the previous analyses which demonstrated that when cognitive scores for offspring born after MAR offspring were compared with those of their naturally conceived peers, in a richly characterized UK cohort up to the age of 11 years, there was no evidence that children born after MAR were cognitively disadvantaged.[6] Analyses are extended to cognitive scores at 14 years and MAR offspring are stratified into LBW and non-low-birthweight (NLBW) groups to assess the impact of MAR and LBW together on cognitive scores.[5]

The comparisons of cognitive scores demonstrate that MAR LBW offspring perform more like naturally

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conceived NLBW children on cognitive tests up to age 14 years. Though not the primary hypothesis, results also show that MAR LBW offspring do perform less well than MAR NLBW children, but outperform naturally conceived LBW children at each time point. After adjusting for just one early-life proxy measure of parental socio-economic status, namely maternal education when the cohort offspring are 6 months old, any apparent cognitive-score differences between the different conception and birthweight groups are attenuated, with the scores converging over time.[5]

So what do these new analyses add to our understanding of the impact of MAR on life-course cognition and future wellbeing for the increasing number of offspring born after these complex and evolving MAR interventions.

These new findings support the importance of the social context for childhood cognitive development. Differences in scores between stratified groups reinforce that cognition is the result of more than differential rates of growth *in utero*.[7]

Even within the MAR group, there is some evidence that being born LBW may be associated with minor cognitive disadvantage relative to being MAR and NLBW. However, the impact of reduced fetal growth does not appear to be as important as the impact of parental social disadvantage on childhood cognition scores overall. Being born LBW after MAR is not associated with the same cognitive disadvantage as being born LBW after natural conception.[5]

Only a singular measure is used to proxy for parental socio-economic status, but this is sufficient to attenuate the differences observed in cognitive scores between offspring stratified by conception type and birthweight in the Cozzani *et al.* study. However, it is likely that the real impact of socio-economic advantage on childhood outcomes, including cognition, occurs because of cumulative exposure to a clustered set of interdependent social and biological factors operating over time. The set of factors may be highly correlated with the singular early-life measure of maternal education, but a single proxy measure will rarely fully capture their diversity or temporal ordering.[8]

In general, cognitive scores reflect the cumulative impact of the richness of the perinatal and postnatal environments available to children during their early years.[9] These influences go beyond a proxy measure of maternal education, and also beyond financial resources, to encompass access to opportunities and social resources that can support cognitive development within the family and within wider informal and formal societal groupings. It is likely that not being able to fully characterize the complexity of the social environment that offspring experience over time, by using only one proxy measure of socio-economic status, has contributed to the delay in attenuation of differences in cognitive scores between groups over time until they have entered adolescence. Exploring the impact of MAR on the development of cognition should properly use individual trajectories of cognitive development that could be considered together with exposures to changing social environments, rather than treating cognitive scores at different ages as if they are independent of each other.[10,11]

Overall, this study has offered reassurance that MAR not only helps some families to cope with subfertility; it currently also does not increase the burden of social and economic costs that have been associated over the life course with poor perinatal outcomes. However, this reassurance appears to be largely the result of MAR being selectively available to parents whose background social advantages more than compensate for the impact of any poor perinatal outcomes after MAR.

A fuller life-course methodological approach acknowledging the complexity of the social environment and trajectories of cognitive development over time is required if analyses are to have the utility to inform relevant strategies to ensure that, if MAR does become more equitably available to all parents who experience subfertility, postnatal benefits also accrue equally to offspring regardless of background parental social status .

Conflict of interest

None declared.

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