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INVITED COMMENTARY

Children conceived by ART grow differently in early life than naturally conceived children but reach the same height and weight by age 17. Reassuring? Not so sure

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Assisted Reproductive Technologies (ART) has brought incredible joy to those who have been confronted with an unfulfilled wish for a child. The success of ART is undeniable with the birth of 8 million human beings who would not have existed without these techniques. Most ART children appear healthy, but despite the large numbers of individuals conceived through these techniques, we have only limited insight into the long-term effects of these techniques on the growth, development and health outcomes of this ever increasing group of human beings (Roseboom, 2018). This insight would be relevant to inform couples and the health care system about the potential risks of these treatments for the long-term health of these children, and especially if any such potential risks would be linked to modifiable elements of the treatment itself which could make future treatments not only more effective but also safer in the long run.

Increasingly, we are realizing the implications of the biological fact that, like all living creatures, human beings are sensitive to the early environment in which they grow and develop. Environmental exposures during critical periods of human development, including the periconception period in which massive epigenetic reprogramming takes place and germ layers are being formed, have long lasting consequences for subsequent development and growth and thereby impact later health (Fleming *et al.*, 2018). Embryo culture conditions can modulate the developmental programme in animal models. There is evidence of embryo culture altering the allocation of cells to trophectoderm and inner cell mass (Watkins *et al.*, 2007; Chen *et al.*, 2019), affecting embryo metabolism and epigenetic regulation of the embryonic genome, leading to altered growth trajectories and adaptations in cardiovascular development that result in elevated blood pressure and glucose intolerance (Watkins *et al.*, 2007; Rexhaj *et al.*, 2013; Chen *et al.*, 2014; Feuer *et al.*, 2014).

The human embryo is also affected by its environment, as the composition of the culture medium and cryopreservation have been shown to affect size at birth (Kleijkers *et al.*, 2016; Zaat *et al.*, 2021). Whether the environment of little embryos have equally big implications for human development and long-term health is unknown. The experimental studies needed to establish causality would require large numbers in order to detect subtle differences. The few RCTs in human ART that have studied long term health outcomes have been underpowered and were unable to detect potential subtle differences in health (Mintjens *et al.*, 2019).

Large register-based longitudinal cohort studies are important because the use of registries limits selection bias, and the large numbers of individuals with detailed information not only boosts statistical power to detect subtle differences but also allows analyses to be adjusted for potential confounding factors. An excellent example of such a study is the Norwegian Mother, Father and Child Cohort Study, the MoBa cohort, which is featured in this issue of *Human Reproduction* (Magnus *et al.*, 2021).

In their article, Magnus *et al.* present findings from a large-scale population based longitudinal study using detailed information on thousands of individuals from conception to age 17 years, showing that children conceived through ART grow differently in early life than naturally conceived children (Magnus *et al.*, 2021). ART children are born smaller but grow faster after birth resulting in increased height and weight at the age of 3 years, while in subsequent years the difference in height and weight from naturally conceived children diminishes until,

at age 17 years, no differences are apparent. Children born to subfertile parents had similar growth patterns as children born after ART, suggesting that at least part of the difference in growth pattern among children conceived by ART may be due to factors underlying parental fertility problems. However, elements of the ART procedure also contribute to the differences in growth patterns, as children conceived by frozen embryo transfer tended to be larger at week 18 of pregnancy and continued to be bigger up to age six. These differences, too, were not present at age 17 years.

This study is important as it provides answers to important questions about later growth and development of a large group of ART children. The study design has several strengths including the large sample size, the longitudinal design, as well as the registry based approach limiting selection, and providing the ability to adjust for potential confounders such as parental body size as an important marker of the underlying genetic growth potential. The large sample size and detailed information on potential confounders also allowed sub-group analyses looking at within family differences, as well as allowing for the comparison of ART with naturally conceived children from sub-fertile parents to exclude effects of infertility on outcome and importantly also allowed for analyses of particular elements of the ART treatment itself, giving indications of potentially modifiable factors in the treatment that would allow for further optimization of treatment.

Because ART children reach the same height and weight at the age of 17 as their naturally conceived peers, the authors conclude that the findings are reassuring. Although similar height and weight at age 17 suggests that ART children are just like any other children, we are not quite sure whether we should rest assured.

Although gross body size is similar, there may be important differences in body composition (Yajnik and Yudkin, 2004) which is of major importance for metabolic health. Moreover, the growth patterns of ART children are strikingly similar to patterns of growth that have been shown to characterize children who develop type 2 diabetes and cardiovascular disease later in life (Eriksson *et al.*, 2001; Bhargava *et al.*, 2004; Barker *et al.*, 2005; Eriksson *et al.*, 2006). Children who grew slowly in foetal life, as evidenced by repeated ultrasounds, and who were born small but subsequently gained weight rapidly in childhood had poorer cardiometabolic risk biomarkers at the age of 2 years (Ong *et al.*, 2020). This may suggest that ART children, despite their apparently similar size in early adulthood, may be on the road to developing type 2 diabetes and cardiovascular disease in later adulthood. Both animal experimental evidence as well as observational evidence in humans suggest that ART children are at such an increased risk. Children conceived through ART have cardiovascular changes that can already be detected during foetal development and persist into childhood. These cardiovascular changes include larger atria, more globular ventricles and signs of systolic and diastolic dysfunction as well as higher systolic and diastolic blood pressure (Valenzuela-Alcaraz Serafini *et al.*, 2019). Many other cohorts have reported vascular impairment and raised blood pressure in ART children (Ceelen *et al.*, 2008; Sakka *et al.*, 2010; Scherrer *et al.*, 2012; Guo *et al.*, 2017) and susceptibility to metabolic dysfunction including impaired glucose metabolism (Sakka *et al.*, 2010; Chen *et al.*, 2014; Gkourogianni *et al.*, 2014; Pontesilli *et al.*, 2015; Guo *et al.*, 2017) and altered body fat distribution, despite similar height and weight (Ceelen *et al.*, 2007).

Considering the evidence of long-term consequences of ART in animal models and human cohorts combined with the patterns of growth from birth to early adulthood that are being reported by Magnus *et al.*, we cannot rest completely assured. Indeed, as the authors write, more information is needed on long-term cardiometabolic health in children born after ART. Although most ART children are too young to study overt disease now, we will need to continue following how they develop into older age and include more deep phenotypic measures before we know whether or not we can rest assured. Studies like the MoBa cohort will be essential to continue assessing the long-term health consequences of ART. Ideally, registers on the health of ART children could help get the insight into any potential long-term consequences of ART for later health. In the meantime, new ART techniques should not be introduced into the clinic without proper surveillance to track the later health of individuals conceived through these techniques. The millions of individuals conceived through these techniques, as well as their parents, have the right to health, and we as a scientific community have the responsibility to inform them about what we do and do not know about the potential risks associated with the treatment that has fulfilled these peoples' wish to have a child.

In order to prevent cardiovascular and metabolic diseases in ART children, the beneficial effects of healthy lifestyle choices including physical exercise should be emphasized since those who were small at birth benefit most from health effects of exercise (Eriksson *et al.*, 2004).

Data availability

Since the article does not include original data, no data are available.

Authors' roles

T.J.R. drafted the manuscript and J.G.E. provided comments and suggestions.

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Conflict of interest

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