



# Reproductive outcomes in women and men conceived by assisted reproductive technologies

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Cite this as: *BMJMED* 2023;2:e000547. doi:10.1136/bmjmed-2023-000547

Received: 13 March 2023  
Accepted: 27 March 2023

Men and women who were conceived by assisted reproductive technology and become parents do not appear to be at increased risk of adverse pregnancy outcomes

Assisted reproduction technologies (ART) include any treatments related to fertility in which eggs or embryos are manipulated to attain a pregnancy, including in-vitro fertilisation and intracytoplasmic sperm injection.<sup>1</sup>

The first baby born by in-vitro fertilisation was in 1978, which was the starting point of ART worldwide. More than 10 million children have since been born in the past 40 years. The use of ART is rapidly increasing, with the total number of ART cycles exceeding three million annually and resulting in almost 500 000 babies born every year.<sup>2</sup> The proportion of babies born from in-vitro fertilisation varies from 2-4%, with the highest percentages in Australia and New Zealand.<sup>3</sup> A substantial proportion of people conceived by ART are now of reproductive age and are becoming parents, which raises the question as to whether they have an increased risk of adverse reproductive and pregnancy outcomes.

Even though ART has been associated with adverse obstetric outcomes and perinatal complications,<sup>4</sup> the long term health outcomes and reproductive potentials of children born by use of ART are little known.<sup>5 6</sup> Children born with ART appear to have an increased risk of developing cardiovascular diseases in the future but further evidence is needed.<sup>6 7</sup> The findings for neurobehavioural disorders are ambiguous but the data for cancer risk are reassuring.<sup>8</sup> Despite concerns regarding the social development of children conceived by ART, a large longitudinal study showed that these children do not suffer from worse psychosocial health compared with naturally conceived children.<sup>9</sup> Strong evidence links ART with epigenetic changes in the newborn baby that suggest impacts on later health outcomes; however, larger studies in adulthood are required to test this hypothesis.<sup>10</sup> The pubertal development, measured by Tanner's classification, age at menarche, menstrual cycle characteristics, bone age, and concentrations of sex hormone, appear to be reassuringly similar between in-vitro fertilisation and children in the control group.<sup>11</sup> Yet, the association of ART with the reproductive outcomes of individuals born by ART methods is not yet fully described. To address this gap, Carlsen and colleagues in the linked article by *BMJ Medicine* report the findings of the first study to examine this association.<sup>1</sup>

Carlsen and colleagues analysed data from the Norwegian Medical Birth Registry and included all

women and men born in Norway from 1984 (which was the year of the first baby born who was conceived by ART in Norway) to 2002, which accounted for just more than one million people. The authors then followed up this population up to 2021 and identified all registered pregnancies linked to these women and men. They included all pregnancies with live born babies, miscarriages (defined as fetal loss between 12 and 22 weeks of gestation), and abortions undertaken at 12-22 weeks of gestation. Pregnancy and perinatal outcomes of these pregnancies were examined and compared between individuals who were conceived by ART and those conceived naturally.

Almost 1% of the girls and boys born in Norway between 1984 and 2002 were conceived by ART. The likelihood of people who were conceived by ART of becoming parents was lower compared with people who were naturally conceived (hazard ratio 0.88 (95% confidence interval) 0.81 to 0.96) for women and 0.91 (0.83 to 1.01) for men); however, they did not account for social and medical factors that might alter the decision for reproduction. Obstetric and perinatal outcomes, including hypertensive disorders, lower birth weight, earlier gestational age at birth, congenital malformations, and admission to neonatal intensive care unit, were similar between parents conceived by ART or naturally and the results were adjusted for parental age at conception. However, a slightly increased risk of lower 5 min Apgar score for newborn babies born by women conceived by use of ART was noted.

One of the main strengths of this study is the comprehensive inclusion of all births in Norway between the first year of a child born from use of ART from 1984 to 2002 and all registered pregnancies and birth of this population up until the end of 2021. Another strength is the clear definition of ART, which included any use of ART (fresh and frozen embryo transfer), and in-vitro fertilisation with and without intracytoplasmic sperm injection. They excluded intrauterine inseminations or people with a history of isolated incidences of subfertility. Potential weaknesses include the small number of pregnancies by individuals conceived by ART and that the results might not be generalisable to other more diverse populations. Another limitation was that the people in this study were on average younger compared with the mean age at first pregnancy for Norwegians. Therefore, when interpreting the findings of this study, the reader should consider that poor perinatal outcomes are more common with increased age.<sup>12</sup> Early miscarriages before 12 weeks of gestation were not measured, which could explain the smaller rate

of first time register pregnancy for people conceived by ART. Additionally, socioeconomic factors and chronic conditions were not accounted for, which could affect an individual's decisions and ability to conceive.

What can be learnt from this study? Evidence suggests that individuals conceived by ART are not associated with an increased risk of worse pregnancy or perinatal outcomes compared with naturally conceived people. Those conceived by ART appear to conceive less often; however, when factoring in their backgrounds, this association weakens, whereas social and medical or other residual factors were not measured, which might weaken further this association by altering the fertility wishes of individuals. Larger studies with longer follow-ups are needed of women and men throughout their reproductive period to offer adequate reassurance that the parental mode of conception is not associated with fertility challenges or adverse pregnancy and perinatal outcomes.

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**Contributors** TD interpreted the results and wrote the first draft. SI provided important insight and critically revised the manuscript. All authors have contributed to data interpretation, editing of the manuscript, and final approval of the manuscript.

**Funding** The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

**Competing interests** We have read and understood the BMJ policy on declaration of interests and declare the following interests: none.

**Provenance and peer review** Commissioned; not externally peer reviewed.

**Data availability statement** Data sharing not applicable as no datasets generated and/or analysed for this study.

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