



Cancer Risk Among Children Born After Fertility Treatment

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Using information from the French National Mother-Child Register, Rios et al¹ assess the risk of childhood cancer among more than 8.5 million children born between 2010 and 2021 (with follow-up to June 2022) by comparing those born after fertility treatment with those conceived naturally. The authors found no overall increased risk of any childhood cancer among children born after fertility treatment with artificial reproduction technologies (ART; ie, fresh embryo transfer [ET] and frozen embryo transfer [FET]) and artificial insemination. However, in analyses of specific cancer types, children born after FET had an increased risk of acute lymphoblastic leukemia (ALL), with a hazard ratio (HR) of 1.61 (95% CI, 1.04-2.50). Furthermore, in an analysis of a restricted cohort of children born between 2010 and 2015, the risk of leukemia was also significantly increased among children born after fresh ET, with an HR of 1.42 (95% CI, 1.06-1.92). The major limitations of studies published to date include small sample sizes, leading to imprecise risk estimates, and self-reported retrospectively collected data, leading to potential recall bias. The study by Rios et al is the largest to date based on high-quality registry data and thus adds great value to the published literature.

Although childhood cancer is rare and treatment has greatly improved, it remains one of the most common causes of death among children. Few modifiable risk factors are well-established, except for ionized radiation and prior chemotherapy,² and it remains unknown why the incidence of childhood cancer seems to have increased worldwide since the 1980s.³ The first birth after in vitro fertilization (IVF) occurred in 1978; since then, it is estimated that more than 10 million children have been conceived via ART globally. Use of ART has been linked with several detrimental perinatal outcomes among children, including preterm birth and congenital malformations; disturbingly, several high-quality studies and systematic reviews have reported increased cancer risk among children born after fertility treatment.⁴

In accordance with findings from a 2019 systematic review and meta-analysis⁴ and a 2022 large registry-based study from Taiwan,⁵ Rios et al¹ observed an increased risk of leukemia but not of any type of childhood cancer. Different childhood cancer types likely have different etiologies; however, associations with ART have been reported for several other childhood cancers, including hepatoblastoma, neuroblastoma, retinoblastoma, tumors of the central nervous system, and sarcoma. Leukemia is the most common childhood cancer type and investigating other types is difficult because of their rarity. Hence, although accumulating evidence seems to indicate an increased risk mainly for leukemia, studies may be statistically underpowered to show associations for the rarer cancer types.

In analysis of the entire cohort, Rios et al¹ observed an increased risk of ALL among children born after FET. However, they also found an increased risk of leukemia among children born after fresh ET in the restricted cohort (2010-2015), with longer follow-up and at a time when fresh ET was more common than FET. It is curious why the authors did not report a common estimate for ART (including both fresh ET and FET). However, if these associations are confirmed, they suggest that factors related to both ART types (FET and fresh ET) may confer the observed risk. Fertility drugs and culture media are used in both FET and fresh ET; however, like most other studies, Rios et al¹ did not have information on these factors. Also, the authors did not have information on the specific ART procedures used (eg, IVF and intracytoplasmic sperm injection). More detailed exposure information in future studies would aid in elucidating the potential underlying mechanisms between ART and childhood cancer risk.

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Rios et al¹ rightly raised the concern that it is unknown whether the increased leukemia risk observed in their study may, in fact, be attributable to factors related to the underlying infertility rather than the fertility treatment. Nevertheless, other high-quality studies with information on maternal infertility have reported increased cancer risk among children born after ART, even when using a reference group of children born to mothers with fertility problems who did not use ART.^{5,6} Although no statistically significant difference was found in the study by Rios et al, investigators in a large Nordic study including data from Denmark, Norway, Sweden, and Finland found an increased risk of cancer (and also of leukemia) among children when comparing FET with fresh ET.⁷ These findings suggest that factors related to the underlying infertility do not explain childhood cancer risk associated with ART.

The study by Rios et al¹ is the latest among several high-quality studies to report an increased risk of leukemia among children born after ART. More large high-quality studies are needed (1) to corroborate the accumulating evidence of increased cancer risk among children after ART and (2) to investigate what aspects of ART may confer higher risk. With an increasing number of children being born after ART use, this risk becomes progressively easier to investigate as more childhood cancer cases become available for study. Likewise, the increasing number of children being born after these procedures highlights the imperativeness and importance of these studies. Until then, it should be considered whether the accumulating evidence to date is enough to put fertility treatment on the still short list of modifiable risk factors for leukemia in children.

ARTICLE INFORMATION

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