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Cancer risk in a nationwide cohort of children and young adults conceived by assisted reproductive technology in 1983-2012

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Study question:
Are children conceived by assisted reproductive technology (ART) at increased cancer risk, compared with the general population and with non-ART conceived offspring from subfertile women?

Summary answer:
Overall cancer risk was not increased in ART-conceived offspring compared with non-ART conceived offspring from subfertile women (median follow-up, 17 years).

What is known already:
There is growing evidence that ART procedures could perturb epigenetic processes during the pre-implantation period. Although the results of most studies are reassuring for children born after in vitro fertilization (IVF), recent studies showed (non-)significantly increased cancer risks after intracytoplasmic sperm injection (ICSI) and frozen embryo transfer (FET). Since the proportion of children born after these techniques increased dramatically over the past decades, it is important from a public health perspective to investigate cancer risk after ICSI and FET in larger studies.

Study design, size, duration:
Data were used from the OMEGA-cohort, a historical nationwide cohort with prospective follow-up in the Netherlands. Offspring of women who were treated in one of the 13 IVF clinics or 2 regional fertility centers between 1983-2012 were included. Of 98,165 live-born children, 53,154 were ART-conceived and 45,211 were non-ART conceived (conceived naturally with or without ovarian hyperstimulation) by subfertile women.

Participants/materials, setting, methods:
Data on type of fertility treatment and maternal risk factors were available from medical records from the mothers and the Dutch Perinatal registry. Cancer incidence was ascertained through linkage with the Netherlands Cancer Registry. Cancer risk in ART-conceived children was compared with risk in children not conceived by ART from subfertile women (hazard ratios [HRs]) and with children from the general population (standardized incidence ratios [SIRs]).

Main results and the role of chance:
The median age at end of follow-up was 17 years and was shorter in ART-conceived children (16.1 years) compared with non-ART children (19.1 years). In total, 382 cancers were observed, 166 in the ART group and 222 in the non-ART group. In preliminary analyses, overall cancer risk was not increased in ART-conceived children, neither compared with children not conceived by ART from subfertile women (HR:0.98, 95% confidence interval (CI)=0.79-1.22) nor compared with the general population (SIR:0.98, 95% CI=0.81-1.11). Risks were also not significantly increased in children conceived by ICSI or FET (HR:1.20, 95%CI=0.85-1.70; 1.25, 95%CI=0.68-2.43, respectively). From 18 years of age onwards, the HR of cancer in ART-conceived versus non-ART individuals was 1.22 (95%CI=0.86-1.74). There were no significantly increased site-specific cancer risks in ART-conceived children compared with non-ART children and the general population. Risk of lymphoblastic leukaemia was not increased in the ART group compared with the non-ART group (HR: 1.03, 95% CI=0.58-1.82).

Limitations, reasons for caution:
Despite the large cohort and long-term follow-up the number of cancer cases was limited which hampered some subgroup analyses, especially for analyses according to specific cancer types and children born after FET.

Wider implications of the findings:
The results from this study importantly contribute to the current knowledge about health risks in ART-offspring. Physicians may inform parents who consider ART about potential health risks for ART-conceived children. Furthermore, pediatric oncologists

caring for ART-conceived children/adolescents with cancer need evidence-based information about the association between ART and cancer risk.

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