GYNECOLOGY: INFERTILITY/REPRODUCTIVE TECHNOLOGIES

The Risks of Birth Defects and Childhood Cancer With Conception by Assisted Reproductive Technology

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Abstract

As the proportion of births conceived with assisted reproductive technology (ART) continues to increase, a growing body of literature continues to examine the risks involved such as the higher risk of birth defects. Recently, several studies have suggested that ART-conceived children may have a greater risk of childhood cancer.

This population-based cohort study aimed to evaluate the risk of childhood cancer as a function of birth defect status and method of conception. Data were obtained from the Society for Assisted Reproductive Technology Clinic Outcome Reporting System, birth certificates (2004–2013), birth defect registries, and cancer registries in 4 states. The Society for Assisted Reproductive Technology Clinic Outcome Reporting System contains comprehensive information on ART procedures from 86% of all clinics and more than 92% of all ART cycles in the United States. Assisted reproductive technology cycles reported from January 2004 to December 2017 that resulted in live births were included in this study. For each ART-conceived delivery, the subsequent 10 deliveries were selected as the non-ART comparison group, and siblings of each ART birth were selected as the ART sibling group. The ART group was divided into 4 subgroups based on the combination of oocyte source (autologous or donor) and embryo state (fresh or thawed). A host of independent variables with established associations on birth defects, cancer, and/or ART were selected a priori for inclusion in statistical models.

The total study population included 165,125 ART-conceived children, 31,524 non-ART siblings, 12,451 children born as a result of infertility treatment without ART (ovulation induction/intrauterine insemination [OI/IUI]), and 1,353,440 naturally conceived children. A total of 29,571 singleton children (2.0%) and 3753 twin children (3.5%) had a major birth defect. Compared with naturally conceived children, risks for defects were increased for all other groups for nonchromosomal (adjusted odds ratios [AORs] ranged from 1.20 to 1.24, except for donor-fresh), blastogenesis (AORs, 1.22–1.74), cardiovascular (AORs, 1.04–1.26), gastrointestinal (AORs, 1.28–2.01), musculoskeletal (AORs, 1.10–1.48), and genitourinary among male children (AORs, 1.15–1.40, except for donor-fresh). Orofacial defects were

increased in the OI/IUI and autologous-fresh and autologous-thawed groups (AORs, 1.26–1.42). The risk of any cancer was increased among ART autologous-fresh and non-ART siblings (hazard ratios [HRs], 1.31 and 1.34, respectively). A total of 127 children had both birth defects and cancer, with 53 (42%) of these children having leukemia. A Cox proportional hazards regression model identified 2 components for the risk of cancer: method of conception and type and number of birth defects. The presence of chromosomal defects was strongly associated with cancer risk (HRs, 8.70 for all cancers and 21.90 for leukemia), and this was further increased in the presence of both chromosomal and nonchromosomal defects (HRs, 21.29 for all cancers, 64.83 for leukemia, and 4.71 for embryonal tumors).

The results of this study demonstrate that compared with naturally conceived children a significantly increased risk of nonchromosomal birth defects was found among children conceived with infertility treatment and that the risk of cancer was increased by greater than 30% among non-ART siblings and ART children born from autologous-fresh cycles. Among both naturally conceived and ART-conceived children, the presence of birth defects was associated with a greater risk of cancer.

EDITORIAL COMMENT

(A growing proportion of the populations of developed countries have been conceived following fertility treatment, especially ART, making it imperative to understand the effects of these interventions on the health of offspring. Some articles suggest ART increases the risk of birth defects, but recent studies have suggested that ART-conceived children also may increase the risk of childhood cancer. This cohort study evaluated the risk of childhood cancer as a function of birth defect status and method of conception using data from the Society for Assisted Reproductive Technology Clinic Outcome Reporting System, birth certificates, birth defect registries, and cancer registries in 4 US states. Each ART-conceived delivery was matched with 10 subsequent deliveries for a non-ART comparison group. Siblings of each ART birth formed an ART sibling group. Four subgroups of the ART group were established according to oocyte source (autologous vs donor) and embryo state (fresh vs thawed). The large study population included 165,125 ART-conceived children, 31,524 non-ART siblings, 12,451 children born following fertility treatment without ART (OI/IUI), and 1,353,440 naturally conceived children; 29,571 singleton children (2.0%) and 3753 twin children (3.5%) exhibited a major birth defect. Compared with naturally conceived children, risks for birth defects were increased for nonchromosomal, blastogenesis, cardiovascular, gastrointestinal, musculoskeletal, and genitourinary among male children. Orofacial defects were increased in children conceived by OI/IUI and autologous-fresh and autologous-thawed groups. The risk of any cancer was increased among ART autologous-fresh and non-ART siblings. A total of 127 children had both birth defects and cancer; 42% had leukemia. A Cox proportional hazards regression model identified 2 risks for cancer: method of conception and type and number of birth defects. The presence of chromosomal defects was strongly associated with cancer risk, and both chromosomal and nonchromosomal defects further increased this risk. This study demonstrates increased risk of nonchromosomal birth defects in children conceived with fertility treatment compared with naturally conceived children.

The risk of cancer also increases in ART-conceived children as well as in non-ART siblings. Birth defects are associated with increased risk of cancer in all groups. Further studies are needed to tease apart the effects of fertility treatment from underlying predisposition on risks of birth defects and cancer in offspring.—DK)