Fertility treatment and childhood cancer risk: a systematic meta-analysis

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Objective: To clarify the association between fertility treatment and the risk for cancer in children.
Design: Meta-analysis.
Setting: None.
Patient(s): Twenty-five cohort and case-control studies involving children born after fertility treatment as the exposure of interest and cancer as the outcome.
Intervention(s): None.
Main Outcome Measure(s): Medline was searched through September 2012 to identify relevant studies. The study-specific estimates for each cancer outcome were combined into a pooled relative risk (RR) with 95% confidence interval (CI) by a meta-analytic approach.
Result(s): We found that children born after fertility treatment were at increased risk for all cancers (RR = 1.33; 95% CI, 1.08–1.63) and for hematological cancers (RR = 1.59; 95% CI, 1.32–1.91), central nervous system/neural cancers (RR = 1.88; 95% CI, 1.02–3.46), and other solid cancers (RR = 2.19; 95% CI, 1.26–3.80). For specific cancer types, we found increased risks for leukemias (RR = 1.65; 95% CI, 1.35–2.01), neuroblastomas (RR = 4.04; 95% CI, 1.24–13.18), and retinoblastomas (RR = 1.62; 95% CI, 1.12–2.35) associated with fertility treatment.
Conclusion(s): The results of the largest meta-analysis on this topic to date indicate an association between fertility treatment and cancer in offspring. However, our results do not rule out that factors related to underlying subfertility, rather than the procedure itself, are the most important predisposing factors for childhood cancer. (Fertil Steril® 2013;100:150–61. ©2013 by American Society for Reproductive Medicine.)
Key Words: Childhood cancer, meta-analysis, fertility treatment

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Remarkable progress has been made in the treatment of infertility during the past five decades. In the 1960s, the antiestrogens clomiphene citrate and tamoxiphen were introduced to induce ovulation in anovulatory women, and the first "test tube" baby was born in 1978 (1). Since then, IVF has progressed from an experimental technique to a routinely used treatment. Further advances in the field have included cryopreservation of embryos, blastocyst transfer, assisted hatching, preimplantation genetic diagnosis, and intracytoplasmic sperm injection (ICSI) (2).

While much has been reported on the short-term outcomes of children born after fertility treatment (e.g., birth weight, multiple births, still and live births), relatively few studies have reported on the potential long-term adverse health effects. Childhood cancer is a possible adverse health effect of fertility treatment; however, although 1%–5% of all children born in developed countries are now conceived by assisted reproductive technology (ART) such as IVF and ICSI (3), few studies have reported the incidence of childhood cancer in this already large and growing population.

Childhood cancer is the second most commont cause of death in children in developed countries, as one in five does not survive (4). Furthermore, studies indicate an increase in the incidence of childhood cancer since the middle of the past century. In Europe, the average yearly increase was 1.1% for the period 1978–1997 (4). The etiology of

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childhood cancer remains largely unclear, but it has been hypothesized that some cancers are initiated during the early stages of fetal development (5). Accordingly, events leading up to and around the time of conception may play an important role and warrant further examination. Of possible note is the fact that diethylstilbestrol, which was prescribed to pregnant women between 1940 and 1971 to prevent complications of pregnancy and was associated with the subsequent development of cancer in children, is structurally similar to the anti-estrogens used for ovulation stimulation (6).

Several isolated reports of cancer in children born after fertility treatment, including ovulation stimulation, IUI, IVF, and ICSI, have been published (7–13). However, few large-scale epidemiological studies are available, and the results are inconsistent. While some studies showed an increased risk for all cancers (14) and various types of cancer including retinoblastoma (15), neuroblastoma (16), leukemia (17–19), and hepatoblastoma (20), many others failed to find an association (21–32) or suggested a decreased risk (21). Of further note is that the studies generally lack statistical strength owing to small sample sizes, given the rarity of the outcome.

One previous meta-analysis of 11 cohort studies published up to 2005 on the association between fertility treatment and risk for childhood cancer (33) found no convincing association. However, this analysis was not exhaustive, as only cohort studies of ART (i.e., excluding studies on hormone treatment) were included. Furthermore, studies with longer follow-up times have since been published. We therefore carried out a comprehensive meta-analysis of studies on all types of fertility treatment and the risk for childhood cancer (overall and specific types), including both cohort and case-control studies. While the previous meta-analysis was based on 11 studies, the present one is based on 25 studies published up to September 2012. Our aim was to provide more definite evidence for an association between fertility treatment and risk for childhood cancer.

MATERIALS AND METHODS

Data Sources and Searches

We systematically searched PubMed (http://www.ncbi.nlm.nih.gov) using the keywords "assisted reproductive technology," "ART," "IVF," "ICSI," "ovarian stimulation," "fertility drugs," "fertility treatment," "subfertility," "fertility," and "cancer," and "children" or "offspring." Citation indices, bibliographies of the articles, and review papers in every paper retrieved were also checked to complete the search. We included only articles published in English. Unpublished studies were not considered. We thus compiled a set of epidemiological studies published between January 1, 1966, and September 15, 2012, on the impact of fertility treatment on the risk of offspring for developing cancer.

Study Selection

We included those studies that met the following criteria: [1] presented original data from cohort or case-control studies; [2] the outcome of interest was clearly defined as cancer in offspring (overall or specific types); [3] the exposure of interest was any kind of medically assisted reproduction (MAR) defined as reproduction achieved through ovulation induction; controlled ovarian stimulation; ovulation triggering; intrauterine, intracervical, intravaginal insemination; and assisted reproductive technology (34). Assisted reproductive technology (ART) is defined as all treatments or procedures that include in vitro handling of oocytes and sperm or embryos for the purpose of reproduction (34). Furthermore, we only included studies that did not use children with other types of cancer as controls and provided relative risk (RR) estimates and their confidence intervals (CIs) or sufficient statistics to calculate them. Odds ratios (ORs) were considered RR estimates for case-control studies (35). In the case of overlapping data, only the most recent study was included in the analysis. When several estimates were available, we used that which was adjusted for the largest number of potential confounders. We also included three studies with a slightly different design—two based on a hypothetical cohort (15, 36) and one based on national statistical data with no systematic follow-up of the cohort (37)—and performed sensitivity analyses by including and excluding these studies.

Data Extraction

The following information was abstracted from each paper: study name, year of publication, country or countries where the study was performed, type of epidemiological study, type of fertility treatment (exposure), types of cancer (outcome), variables used in adjustments, restrictions, quota sampling or matching, and risk estimates. Also, specifically for cohort studies, follow-up time, total number of exposed children, and numbers of observed and expected cases were abstracted. For the case-control studies, the numbers of exposed and unexposed cases and controls were extracted. Tables 1 and 2 list the data abstracted from the cohort studies, and Table 3 lists the data from the case-control studies.

Statistical Analysis

We conducted separate meta-analyses for different cancer outcomes. The main cancer outcomes were all cancers, hematological cancers, central nervous system (CNS)/neural cancers, and other solid cancers (all types of solid cancers not included in the two previous categories). Also, to further explore the association between fertility treatment and specific cancer types, we analyzed the following cancers separately (based on the available studies with the same specific cancer outcome): leukemias, CNS cancers, neuroblastomas, and retinoblastomas. All analyses were conducted separately for all types of MAR and for ART.

Four cohort studies did not report RR estimates for the association between fertility treatment and all cancers (36–39). For these studies, we calculated RRs by applying the appropriate cancer incidence rates from national statistics (40–42) and used the average follow-up time to calculate the expected number of cases. The details of how the number of