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Assisted reproductive technology and the risk of pediatric cancer: A population based study and a systematic review and meta analysis

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ABSTRACT

Background: There is controversy whether exposure to assisted reproductive technology (ART) is associated with increased risk of pediatric cancer.

We aimed at calculating the overall risk of pediatric cancers after ART in a large cohort of exposed women; and to conduct a systematic review and meta- analysis of cohort studies examining overall risk of pediatric cancers after ART.

Methods: All children born in Israel who were members of Maccabi Health Services (MHS) between 1999 and 2016 after ART, were linked to the Israeli Registry of Childhood Cancer (IGS) to identify those with cancer diagnosed before 16 years of age. In parallel we conducted a systematic review and meta-analysis of observational cohort studies with more than 5000 ART- exposed cases that measured pediatric cancer after ART.

Results: In the cohort study, the risk ratio for pediatric cancer after ART in general was 0.95 (95% CI, 0.76–1.19). The RR was 1.09 (95% CI, 0.79–1.48) for IVF treatments. Meta- analysis of 13 cohort studies with a total of 750,138 women exposed to ART (with 1152 pediatric cancers) and 214,008,000 unexposed controls (with 30,458 pediatric cancers) did not reveal increased risk for pediatric cancers (RR 0.99; 95% CI, 0.85–1.15).

Conclusions: Based on very large numbers, ART in general, and IVF in particular, are not associated with overall increased risk of pediatric cancer.

1. Background

More than 8 million children have been conceived worldwide by assisted reproductive technology (ART) [1]. In parallel, pediatric cancer rates appear to have risen [2,3]. There is an ongoing controversy whether children conceived by ART are at an increased risk for pediatric cancers [4]. Results of cohort studies, comparing cancer rates among offspring of women conceived with ART to those conceived naturally, range from showing increased cancer risk [5] to those showing no risk [6], or even a protective effect [7]. Studies differ widely in methodological aspects, such as the length of pediatric follow up and the definitions of ART.

It has been hypothesized that repeated hormonal exposure and/or epigenetic modifications of gene expression activated by the manipulation of the gametes in the laboratory, may underline cancer risk [8]. The controversy surrounding the potential risk of cancer among offspring after ART is of great clinical importance, causing anxiety and fears among vulnerable women who have experienced substantial difficulties in having children.

The objectives of the present study were twofold:

1) To compare cancer risk in a large cohort of children conceived by ART to those conceived without ART.
2) To conduct a systematic review and meta- analysis of all cohort studies examining a potential association between ART and overall subsequent pediatric cancers.

Abbreviations: ART, assisted reproductive technology; IVF, in vitro fertilization; MHS, Maccabi Health Services; IGS, Israeli Registry of Childhood Cancer

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2. Methods

2.1. Population-based cohort study

The study included all children born in Israel between January 1, 1999 and December 31, 2016 who were members of Maccabi Health Services (MHS), the second largest health fund in Israel, insuring over 2 million members.

2.1.1. Setting

Data on all study subjects were extracted from the electronic database of MHS. MHS electronic database includes information on parental demographics, maternal pregnancy and health, the delivery and postpartum period, and infant perinatal health. As of 1999, all pregnancies initiated by ART have been registered in MHS database.

2.1.2. Cohorts

All women 18–45 years of age registered in MHS who underwent an ART treatments, were included in this study. ART was defined as treatments or procedures that include the *in vitro* handling of human sperm, oocytes and or embryos for the purpose of establishing a pregnancy [8]. Ovulation induction *per se* was not included. Further information related to the pregnancies initiated by any ART, included the type of ART used (Intra Uterine insemination (IUI), conventional in vitro fertilization (IVF), intracytoplasmic sperm injection (ICSI), or other forms of treatment [frozen/thawed embryo transfer or performing assisted hatching before embryo transfer).

All individuals registered at MHS as having been conceived by ART were classified as ART-conceived children, and all those without a registered ART conception were defined as unexposed controls. Data were linked to all children born in Israel who were members of MHS between 1999 and 2016 after ART or spontaneously, with data from the Israeli Registry of Childhood Cancer (IGS) to identify all children in whom cancer was diagnosed before 16 years of age.

The two databases—MHS and IGS were encoded and linked by personal identification numbers (numbers that are given at birth by the Interior Ministry and used throughout life) to create a registry of all patients who underwent any form of ART treatment, their pregnancies, pregnancy outcome and the children born from non-ART treatments. The latest complete update of the cancer data was on April 23, 2018. The study was approved by Assuta Hospital research ethics committee in Tel Aviv.

The overall risk of pediatric cancer in Israel was compared to the risk among MHS children conceived by ART. Descriptive statistics and 95% CI were summarized and are presented by groups. Differences between the groups were determined using *T* test or Fisher's exact test as appropriate. Two covariates were defined: age of the mother at birth and smoking. Age was grouped to 25–30; 30–35; above 35 and smoking was defined as ever/never smoked. A logistic regression model was used to compute odds ratios (Ors) and 95% confidence intervals (Cis) for risk of cancer in children conceived by ART compared with those not conceived by ART. All data summaries and statistical analyses were generated using SAS® version 9.3.

2.2. Systematic review and meta-analysis

A systematic review and meta-analysis were conducted including all observational cohort studies that examined the association between ART on cancer in the offspring.

2.2.1. Search Strategy

Search adhering to PRISMA guidelines [9] identified all published articles involving ART exposure during pregnancy and cancer in the offspring. The search included PubMed, EMBASE and Cochrane from inception and till June 1, 2019 for papers published in any language. Subsequently, the references of the identified studies were also reviewed for additional relevant articles.

2.2.2. Study selection

Any published human study that met the following criteria was included in the meta-analysis:

a Observational cohort studies that confirmed in the original article exposure to ART with clear definition of the exposed and control groups. All types of ART were included: Intra uterine insemination (IUI), conventional in vitro fertilization (IV)], intracytoplasmic sperm injection [ICSI], or other forms of treatment (frozen/thawed embryo transfer or performing assisted hatching before embryo transfer). Cases of ovulation induction treatment per se were not included.
b Studies that had sufficient data to identify pediatric cancers in offspring exposed *in utero* to ART. The control group consisted of women who were not exposed to any ART during the index pregnancy.
c Studies with a sample size of at least 5000 pregnancies exposed to ART.

All databases were searched from inception to June 1th, 2019. The *Appendix* presents the terms used in the literature search. Two authors screened the titles and abstracts of all studies identified to determine whether or not they met inclusion criteria (DG and GK). Full text of likely eligible studies was reviewed by the two authors and disagreements were resolved by consensus.

2.2.3. Data extraction

Information collected included the drug name, first author, year of publication, journal name, study design, study location, year of study, whether exposure occurred during the first trimester, type of control, and outcome measures. Outcome measures included the following: pregnant women, live births and pediatric cancers. All the data were arranged in 2 × 2 tables to calculate the RR and 95% CI and the outcomes were considered binary.

2.2.4. Data analysis

Risk data for pediatric cancer were combined with the Review manager Version 5.3, using a random-effect model. Heterogeneity among studies was assessed by Q statistic, which was then quantified by I^2. A significant Q statistic ($P < 0.05$), represents a high degree of variance among the studies. An I^2 value between 0% to 40% might not be clinically important, while between 30% to 60% may represent moderate heterogeneity, between 50% to 90% may represent substantial heterogeneity, and between 75% to 100% considerable heterogeneity [10].

2.2.5. Analysis of potential publication bias

Funnel plots were generated using the Review manager 5.3 software. Funnel plots were visually inspected in order to assess for publication bias [10].

3. Results

3.1. Population based study

The two datasets consisted of 64,317 MHS insured children born after ART and 713,165 MHS-insured children born during the same period who were not conceived by ART. Characteristics of ART-exposed mothers are summarized in Table 1. Overall, 85 cancers were identified in the ART- conceived dataset, as compared with 988 cancers in the non-ART- conceived dataset. This translates to an odds ratio of 0.95 with 95% CI of 0.76 to 1.19. Similarly, in a sensitivity analysis for the cohort consisting of IVF treatments only (including frozen cycles), these treatments were also not associated with an increased risk of any of

Table 1
Cohort study: Characteristics and Numbers of patients exposed to ART and controls, and children's age at cancer diagnosis.

Cancer diagnosis by exposure to ART/ IVF treatment	ART	Controls	IVF
Total number	64,317	713,165	27,193
Number of cancer cases	85	988	41
Age at cancer diagnosis (SD)	4.42 (3.72)	5.34 (4.26)	5.34 (4.26)
% Smoking	5	6	4
Maternal age range (yr.)	18–45	18–45	18–45
Child Followup (mean yr.)	4.1	4.2	4.0

form of cancer. 41 children born after IVF treatments were diagnosed with cancer out of 27,189 IVF fresh and frozen cycles carried out in MHS during the same period of 17 years. (Odds Ratio 1.09; 95% CI, 0.79–1.48). When adjusting for smoking and age of the mother, we did not see any significant change in the results.

3.2. Systematic review and meta-analysis

We identified a total of 17 published papers in peer reviewed journals. After removing studies not containing a minimum of 5000 ART- exposed fetuses, a total of 13 cohort studies [5–7,11–19] (Fig. 1), and the present cohort study fulfilled the inclusion criteria for the meta analysis (Table 2 Fig. 2). All the included studies reported on pediatric cancers in ART- exposed and unexposed children. There was no overlap between studies in terms of reporting on the same ART- pediatric cancer cases.

The 13 cohort studies included a total of 750,138women exposed to ART (with 1152 pediatric cancers) and 21,400,800 unexposed controls (with 30,458 pediatric cancers). The risk of 'pediatric cancer in the offspring of women exposed to RTA was not higher than that of the control population (RR0.99 CI 0.85–1.15)) (Fig. 2). The Q-statistic for heterogeneity of effects was significant ($P < 0.01$, $I^2 = 55\%$) and there was no evidence of publication bias in the funnel plot analysis (Fig. 3). In a sensitivity analysis, after excluding one outlier study [7], there was no heterogeneity and the RR was 0.97(95% CI 0.84–1.12). Repeating the meta- analysis without the present study (Gilboa 2019), as it has not been published yet (but was presented in scientific meetings), y identical results were achieved (RR 0.99, CI 0.85–1.17).

4. Discussion

4.1. Cohort study

A growing number of reports of cancer in children born after fertility treatment have been published, however, only 13 large scale epidemiological studies are available [5–7,11–20]. While some studies showed an increased risk for all cancers [5] others failed to find an association [6] or suggested a decreased risk [7]. In our large population- based cohort study, we did not detect an increase in the overall risk of cancer among Israeli children born after ART during a 17-year follow-up study. This is in agreement with the present meta-analysis showing OR of 0.99.

Several challenges in our cohort study need to be acknowledged. We were not able to investigate some potential mediating factors by means of stratification. Maternal age, but not paternal, have been associated with increased cancer risk [21]. Smoking status have previously been shown not to affect cancer risk in this population [22]. In contrast, maternal fetal loss has been associated with increased risk of offspring leukemia [23]. It is also known that children from multiple births, including those born after assisted conception, are at significantly lower risk than are singletons [24]. The previously identified potential

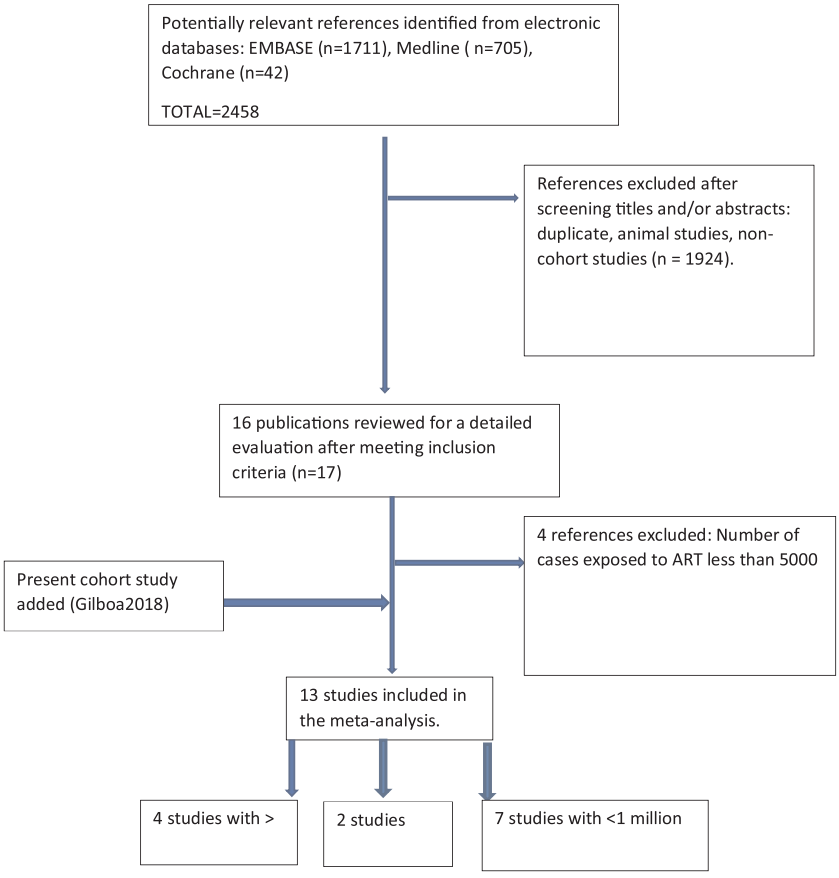

Fig. 1. Flow chart of studisses considered for the meta- analysis.

Table 2
Characteristics of the studies included in the meta- analysis.

First author	Publicationn year	Country	No. ART Exposed	Specific cancers' increased risk	Overall cancer risk
Bruinsma	2000	Australia	5,249		**SIR 1.39(95% CI 0.62–3.03)**
Klip	2001	Netherland	9,484		**SIR 1.0 (0.6–1.7)**
Pinborg	2004	Denmark	5,438		**OR 1.08(0.92–1.28)**
Kallen	2010	Sweden	26,692		**RR 1.42(1.09–1.87)**
Williams	2013	UK	106,013	Hepatoblastoma, Rhabdoblastoma	**SIR 0.98(0.81–1.19)**
Sundh	2014	Sweden	91,796	CNS, Epithelial	**HR 1.08(0.91–1.27)**
Hargreave	2015	Denmark	123,322	ALL, CNS(progesterone)	**No increasedrisk***
Reigstadt	2016	Norway	25,782		**HR 1.21(0.9–1.63)**
Lerner-Geva	2017	Israel	9,042	Retinoblastoma, Renal	**RR 1.18(0.8–1.75)**
Williams	2018	UK	12,137	Hepatoblastoma	**IR 0.83 (0.43–1.45)**
Gilboa	2018	Israel	64,317		**RR 1.09(0.79–1.48)**
Spaan	2019	Netherland	24,269	ALL(N.S.), Melanoma(N.S.)	**HR 1.00 (0.72–1.38)**
Spector	2019	US	275,686	Hepatic	**HR 1.17(1.0–1,36)**

HR: Hazard ratio.
SIR: Standardized incidence ratio.
OR: Odds ratio.
ALL: Acute lymphoblastic leukemia.
CNS: Central nervous system.
N.S.: Non-significant statistically.
*Risk is reported separately for each ART, but no overall figure beyond stating "no increased risk".

mediating factors of low birth weight and premature delivery were not explored in our study.

Our study had an average follow-up of 4 years. Because most cases of many types of childhood cancer occur before 5 years of age, this study provides good evidence that the risk of cancer in children born after ART is not different from the general population. However, for a few diagnostic categories (such as Hodgkin's lymphoma and bone tumors), the peak incidence occurs in later childhood and adolescence. Therefore, a longer follow up cohort needs to be established.

4.2. Meta-analysis

The present systematic review and meta- analysis, based on a total of over 750,138 ART-exposed pregnancies and 21,400,800 controls assembled worldwide by 13 cohort studies up to June of 2019, rules out an overall increased risk for pediatric cancers (Table 2, Fig. 2). We have selected studies that enrolled at least 5000 ART exposed cases; because childhood cancer is rare, smaller cohorts have potentially an inherent increased risk for biased results [4]. Specifically, a study that enrolls only 5000 cases is expected to have only 5 pediatric cancers; the risk of bias of small numbers may be wrongly interpreted.

These findings of our meta- analysis can serve as a reassuring message for families and health care providers trying to conceive. Not only was the overall RR 0.99, the 95% confidence intervals are very tight, and even the highest estimate allows for an increased risk of only 15%.

The different studies differed in their length of follow up of pediatric cancers, however, in most cases the ART-exposed group and control group had comparable length of follow up.

A potential challenge in the present study is in not attempting to address the risk of specific cancers separately. Because of the rarity of most specific pediatric cancers, their reported numbers have been small even in large cohort studies. Several of the studies included in the meta-analysis have addressed specific cancers, finding different trends (Table 2): For example Lerner-Geva et al. suggested increased risks of retinal and renal cancers after ART [17], whereas Reigstad et al. [7] reported increased risk of leukemia. In the Norwegian Register of births, although the authors found an increased risk of leukemia and lymphoma, they concluded that the power of their study and numbers of cancers found was too small to yield a meaningful estimation [7]. Williams et al. reported on the UK National Registry of Childhood Tumors. While there was no increase in the overall risk of cancer among children born after ART during the 17-year study period, they reported increased risks of hepatoblastoma and rhabdomyosarcoma, but the

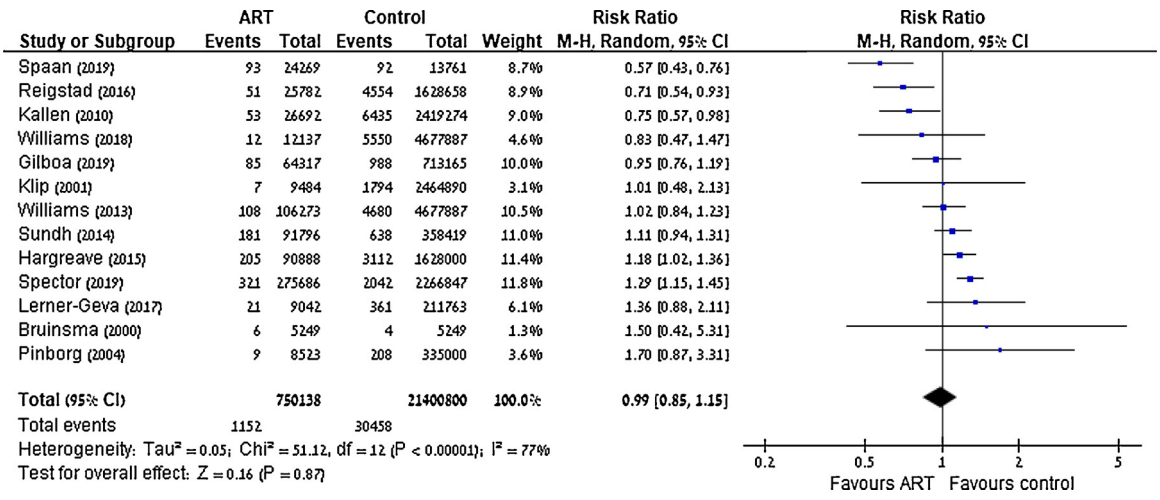

Fig. 2. Meta analysis of cohort studies.

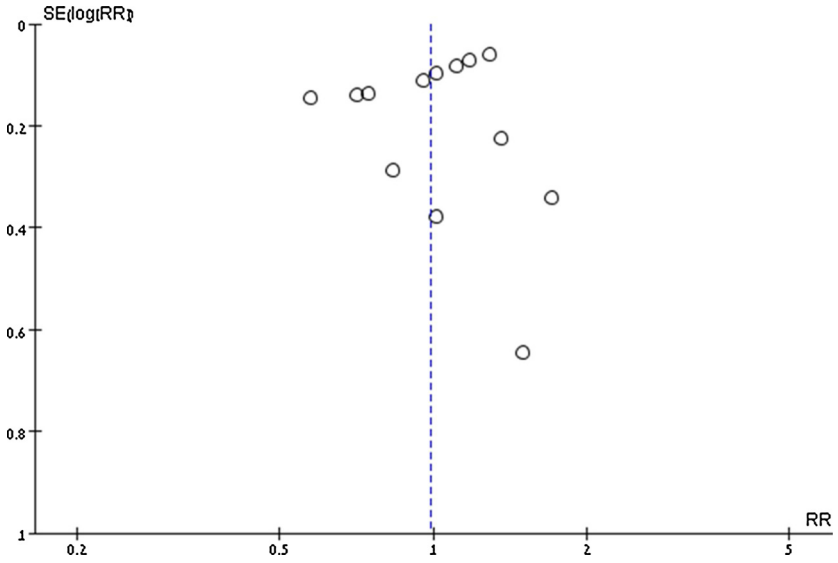

Fig. 3. Funnel plot of studies included in the meta analysis.

absolute risk was very small [6].

Due to their rarity, much larger sample sizes will be needed to address in the future the risks of specific pediatric cancers.

Our meta-analysis included both IVF and non IVF ART. The IVF cases are more worrisome as gametes are manipulated *ex vivo*. However, in our cohort study, analysis of IVF vs. all cases of ART show a similar lack of increased risk of pediatric cancer. These updated results are important because of the steep increase in ART use worldwide and the understandable anxiety of families. It is essential to avoid increasing the anxiety of families based on the results of small underpowered studies [4], and inform these patients on the overall knowledge assembled to date internationally.

Ethics approval and consent to participate

The study was approved by Assuta Hospital Research Ethics Board. Consent to participate- not applicable.

Consent

Not applicable.

Availability of data and materials

All data are stored in Maccabi Research Institute repository and may be accessed upon contact with the PI, pending approval by Maccabi Ethics Board.

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Authors' contribution

G. Koren, E. Lunenfeld and V. Shalev conceived this research project and obtained funding.

D. Gilboa, R. Katz, R. Rotem and G. Koren conducted the population based study.

Y. Barer, D. Gilboa and G. Koren conducted and analyzed the meta analysis.

D. Gilboa and G. Koren wrote the first draft of the paper.

All authors critically reviewed and ammeded the first draft, and approved the final draft.

Declaration of Competing Interest

The authors declare no competing interests.

Acknowledgement

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.canep.2019.101613.

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