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Assisted Reproductive Technology And Risk of Childhood Cancer Among Infertile Parents Offspring

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ADMINISTRATIVE INFORMATION

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Review Stage at time of this submission - Completed but not published.

Conflicts of interest - None declared.

INPLASY registration number: INPLASY202470119

Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 30 July 2024 and was last updated on 30 July 2024.

INTRODUCTION

Review question / Objective P: parental diagnosis of infertility (subfertility); I: ART (including IVF, ICSI, FET, and fresh-ET); C: non-ART; O: childhood overall cancer and childhood-specific cancers.

Condition being studied To date, six meta-analyses have been conducted on the association between ART fertility treatments and childhood cancer risk.The meta-analyses by Wang et al [12], Chiavarini et al [14], and Hargreave et al [10] showed a significant correlation between ART and overall cancer risk in children, while the meta-analyses by Raimondi et al [9], Gilboa et al et al [11] and Zhang et al [13] meta-analyses did not find evidence to support such an association. Recent large-scale cohort studies have also failed to reach a consensus conclusion on this issue. Several studies have found significant associations between ART conception and increased childhood overall cancer risk [19, 21, 30, 37, 38]. For example, the large Nordic study by Sargisian et al. that included data from Denmark, Norway, Sweden, and Finland found that ART-conceived offspring had a significantly increased risk of any type of childhood cancer compared with naturally conceived offspring (HR, 1.13; 95% CI 1.01-1.26). However, other studies have not observed such an association [16, 17, 20]. For example, the study by Rios, based on high-quality registry data, compared the risk of childhood cancer in ART-conceived offspring with that of naturally conceived offspring, and showed that there was no increased risk of childhood cancer in children born after ART conception. Reasons for identifying inconsistencies in the findings of these studies may be related to the selection of the control group, the size of the observational sample size, and the duration of follow-up observations [5, 6, 8, 39].To date, six meta-analyses have been conducted on the association between ART fertility treatments and childhood cancer risk.The meta-analyses by Wang et al [12], Chiavarini et al [14],

and Hargreave et al [10] showed a significant correlation between ART and overall cancer risk in children, while the meta-analyses by Raimondi et al [9], Gilboa et al et al [11] and Zhang et al [13] meta-analyses did not find evidence to support such an association. Recent large-scale cohort studies have also failed to reach a consensus conclusion on this issue.

METHODS

Search strategy pubmed: (((Reproductive Techniques, Assisted[Mesh] OR assisted reproductive technology[Title/Abstract] OR ART[Title/Abstract] OR fertility treatment[Title/Abstract] OR in vitro fertilization[Title/Abstract] OR IVF[Title/Abstract] OR frozen embryo[Title/Abstract] OR ovarian stimulation[Title/Abstract] OR ICSI[Title/Abstract] OR intracytoplasmic sperm injection[Title/Abstract]) AND ((infant[MeSH] OR child[MeSH] OR adolescent[MeSH] OR pediatric[MeSH] OR paediatric[MeSH] OR children[MeSH] OR infant*[Title/Abstract] OR infancy[Title/Abstract] OR child[Title/Abstract] OR childhood[Title/Abstract] OR childhood pediatric[Title/Abstract] OR paediatric*[Title/Abstract] OR adolescen*[Title/Abstract] OR young[Title/Abstract] OR 18 kids[Title/Abstract] OR youth[Title/Abstract] OR juvenile[Title/Abstract] OR preschooler*[Title/Abstract] OR teen[Title/Abstract] OR teens[Title/Abstract] OR teenager*[Title/Abstract]))) AND (("Neoplasms/epidemiology"[Mesh] OR "Tumor*"[tiab] OR "cancer*"[tiab] OR "Neoplas*"[tiab] OR "carcino*"[tiab] OR "malignan*"[tiab] OR "onco*"[tiab] OR "hematoonco*"[tiab] OR Neuroblastoma OR Neuroectodermal Tumors, Primitive OR astrocytoma OR glioblastoma OR DIPG OR glioma OR medulloblastoma OR sarcoma OR osteosarcoma OR ewing OR ewings OR rhabdomyosarcoma OR wilms OR nephroblastoma OR retinoblastoma OR medulloblastoma OR teratoma OR germinoma OR dysgerminoma OR seminoma OR gonadoblastoma OR glioma OR carcinoma OR leukem* OR leukaem* OR lymphoma* OR leucocythaemia OR myelodysplastic syndrome OR myeloproliferative OR hodgkin disease OR HGG OR LGG OR ATRT OR PNET OR CML OR ALL OR AML OR JMML))) AND (("Risk"[Mesh] OR "Risk Assessment"[Mesh] OR "Risk Factors"[Mesh] OR "Odds Ratio"[Mesh] OR "Incidence"[Mesh] OR "Prevalence"[Mesh] OR "Probability"[Mesh:noexp] OR "Epidemiologic Studies"[Mesh] OR risk[ti] OR odds[ti] OR likelihood[ti] OR incidence[ti] OR prevalence[ti] OR propensit*[ti] OR probabilit*[ti] OR frequen*[ti] OR correlat*[ti] OR connect*[ti] OR epidemiolog*[ti] OR associat*[ti] OR relate*[ti] OR relationship[ti] OR "registries"[MeSH Terms]))

EMBASE: ('Reproductive Techniques, Assisted'/exp OR 'assisted reproductive technology':ab,ti OR 'ART':ab,ti OR 'fertility treatment':ab,ti OR 'in vitro fertilization':ab,ti OR 'IVF':ab,ti OR 'frozen embryo':ab,ti OR 'ovarian stimulation':ab,ti OR 'ICSI':ab,ti OR 'intracytoplasmic sperm injection':ab,ti) AND ('infant'/exp OR 'child'/exp OR 'adolescent'/exp OR 'pediatric'/exp OR 'paediatric'/exp OR 'children'/exp OR infant*:ab,ti OR infancy:ab,ti OR child:ab,ti OR childhood:ab,ti OR childhood pediatric:ab,ti OR paediatric*:ab,ti OR adolescen*:ab,ti OR young:ab,ti OR 18 kids:ab,ti OR youth:ab,ti OR juvenile:ab,ti OR preschooler*:ab,ti OR teen:ab,ti OR teens:ab,ti OR teenager*:ab,ti) AND ('Neoplasms/epidemiology'/exp OR 'Tumor*':ab,ti OR 'cancer*':ab,ti OR 'Neoplas*':ab,ti OR 'carcino*':ab,ti OR 'malignan*':ab,ti OR 'onco*':ab,ti OR 'hematoonco*':ab,ti OR 'Neuroblastoma':ab,ti OR 'Neuroectodermal Tumors, Primitive':ab,ti OR 'astrocytoma':ab,ti OR 'glioblastoma':ab,ti) AND ('Risk'/exp OR 'Risk Assessment'/exp OR 'Risk Factors'/exp OR 'Odds Ratio'/exp OR 'Incidence'/exp OR 'Prevalence'/exp OR 'Probability'/exp OR 'Epidemiologic Studies'/exp OR risk:ab,ti OR odds:ab,ti OR likelihood:ab,ti OR incidence:ab,ti OR prevalence:ab,ti OR propensit*:ab,ti OR probabilit*:ab,ti OR frequen*:ab,ti OR correlat*:ab,ti OR connect*:ab,ti OR epidemiolog*:ab,ti OR associat*:ab,ti OR relate*:ab,ti OR relationship:ab,ti OR 'registries':ab,ti)

Cochrane Central Register of Controlled Trials: #1 MeSH descriptor: [Reproductive Techniques, Assisted] explode all trees
#2 ("assisted reproductive technology" or "ART" or "fertility treatment" or "in vitro fertilization" or "IVF" or "frozen embryo" or "ovarian stimulation" or "ICSI" or "intracytoplasmic sperm injection"):ti,ab,kw (Word variations have been searched)
#3 #1 or #2
#4 MeSH descriptor: [infant] explode all trees
#5 MeSH descriptor: [child] explode all trees
#6 MeSH descriptor: [adolescent] explode all trees
#7 MeSH descriptor: [pediatric] explode all trees
#8 ("infant" or "infancy" or "child" or "childhood" or "childhood pediatric" or "paediatric" or "adolescen" or "young" or "juvenile" or "teenager"):ti,ab,kw (Word variations have been searched)
#9 #4 or #5 or #6 or #7 or #8
#10 MeSH descriptor: [Neoplasms] explode all trees
#11 ("Tumor" or "cancer" or "Neoplas" or "carcino" or "malignan" or "onco" or "hematoonco" or

"Neuroblastoma"):ti,ab,kw (Word variations have been searched)
#12 #10 or #11
#13 MeSH descriptor: [Risk] explode all trees
#14 MeSH descriptor: [Risk Assessment] explode all trees
#15 MeSH descriptor: [Risk Factors] explode all trees
#16 MeSH descriptor: [Odds Ratio] explode all trees
#17 MeSH descriptor: [Incidence] explode all trees
#18 MeSH descriptor: [Prevalence] explode all trees
#19 MeSH descriptor: [Probability] explode all trees
#20 MeSH descriptor: [Epidemiologic Studies] explode all trees
#21 ("risk" or "odds" or "likelihood" or "incidence" or "prevalence" or "propensit" or "relationship" or "registries"):ti,ab,kw (Word variations have been searched)
#22 #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21
#23 #3 and #9 and #12 and #22
Web of Science: #1 TS=("Reproductive Techniques, Assisted" or "assisted reproductive technology" or "ART" or "fertility treatment" or "in vitro fertilization" or "IVF" or "frozen embryo" or "ovarian stimulation" or "ICSI" or "intracytoplasmic sperm injection")
#2 TS=("infant" or "infancy" or "child" or "childhood" or "childhood pediatric" or "paediatric" or "adolescen" or "young" or "juvenile" or "teenager")
#3 TS=("Neoplasms" or "Tumor" or "cancer" or "Neoplas" or "carcino" or "malignan" or "onco" or "hematoonco" or "Neuroblastoma")
#4 TS=("risk" or "Risk Assessment" or "odds" or "likelihood" or "incidence" or "prevalence" or "propensit" or "relationship" or "registries" or "Epidemiologic Studies")
#1 and #2 and #3 and #4.

Participant or population P: parental diagnosis of infertility (subfertility).

Intervention I: ART (including IVF, ICSI, FET, and fresh-ET).

Comparator C: non-ART.

Study designs to be included Cohort and case-control studies.

Eligibility criteria Inclusion criteria were as follows: 1) studies on ART (including IVF, ICSI, FET, and fresh-ET) and the risk of childhood cancers; 2) inclusion of only people with a parental diagnosis of infertility (subfertility); 3) cohort studies or case-control studies; and 4) provided sufficient information to calculate RR estimates and their 95% confidence intervals (CIs). Conference abstracts, reviews, non-English language, duplication of research data, and non-peer-reviewed articles were excluded.

Information sources PubMed, EMBASE, Cochrane, and Web of Science.

Main outcome(s) The primary outcome of this study was childhood overall cancer.

Additional outcome(s) secondary outcome was childhood-specific cancers (e.g., leukemia, lymphoma, brain cancer, embryonal tumors, retinoblastoma, and neuroblastoma).

Quality assessment / Risk of bias analysis The Newcastle–Ottawa Quality Assessment Scale (NOS) was used for the quality assessment of the included studies[24]. Disagreements were resolved through discussions with the corresponding author. Low (total score ≥ 7), moderate (total score 5-6), and high (total score ≤ 4) risk of bias.
The results of studies with ≥10 included studies were analyzed for publication bias by funnel plot. If the distribution of points on the funnel plot was symmetrical, it indicated no or low bias; if it was asymmetrical, it indicated the presence of publication bias. Egger's test was used to quantitatively analyze publication bias, and $p < 0.05$ indicated significant publication bias. Moreover, Sensitivity analyses were performed on the primary outcome.

Strategy of data synthesis RR and 95% CIs were chosen to assess the association between ART and childhood cancer in infertile offspring. Outcomes were combined using the DerSimonian and Laird random effects model [25]. All analyses were visualized using Stata 17 statistical software, and in meta-analyses, $p < 0.05$ was considered statistically significant. Heterogeneity was analyzed using the I2 statistic. A high degree of heterogeneity was indicated if the I2 statistic was greater than 50% [26].

Subgroup analysis Regardless of the level of heterogeneity, meta-analysis was performed using the random effects model. Subgroup analyses: 1) continents; 2) Duration of follow-up; 3) Unexposed population; 4) Reported cancer type. Subgroup comparisons were made using the Q-test, and variables between subgroups were considered

significant when the P-value for the subgroup difference was less than 0.05.

Sensitivity analysis Sensitivity analyses were performed on the primary outcome.

Country(ies) involved China.

Keywords Assisted Reproductive Technology, childhood cancer, infertility, subfertility, risks.

Contributions of each author

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