







Reproductive epidemiology

Sex differences in childhood cancer risk following ART conception: a registry-based study

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ABSTRACT

STUDY QUESTION: Does the risk of childhood cancer following ARTs vary by sex?

SUMMARY ANSWER: In this registry-based study, some childhood cancers showed positive sex- and age-specific associations in children conceived using certain ART modalities, which were not evident in overall combined analyses.

WHAT IS KNOWN ALREADY: The relationship between ART and risk of childhood cancer has shown diverse outcomes in prior research. Studies examining whether there are sex differences in childhood cancer risk after ART conception are lacking.

STUDY DESIGN, SIZE, DURATION: This registry-based cohort study included all children born in Norway between 1984 and 2022 ($n = 2\,255\,025$), followed until 31 December 2023.

PARTICIPANTS/MATERIALS, SETTING, METHODS: Children were identified via the Medical Birth Registry of Norway, and information was extracted on whether they were conceived via ART (defined as IVF/ICSI). Of the 2 255 025 children included in the study, 53 694 were ART-conceived. Birth records were linked to the Cancer Registry of Norway. Childhood cancer was defined as a cancer diagnosis according to the International Classification of Childhood Cancer Third Edition (ICCC-3) before the age of 18 years. Cox regression models were used to estimate the age- and sex-specific risk of cancer for ART-conceived children compared to children not conceived via ART.

MAIN RESULTS AND THE ROLE OF CHANCE: Among all children, 0.25% had a cancer diagnosis before the age of 18 years. The cumulative incidence of cancer was higher in children conceived by ART (IVF/ICSI) than in those not conceived via ART (21.5 vs 17.5 per 100 000 person-years, $P = 0.04$), and especially higher in boys conceived with ICSI or after cryopreserved embryo transfer. When combining all age groups, both sexes and all cancer types, there was little evidence of increased cancer risk with ART (adjusted hazard ratio (aHR) 1.13, 95% CI 0.94–1.36). However, differences were found when stratifying by age and sex. From age 5–9 years, ART-conceived children had a higher overall risk of cancer (aHR 1.53, 95% CI 1.06–2.20), with a slightly higher estimate in boys (aHR 1.73, 95% CI 1.09–2.74), than in girls (aHR 1.28, 95% CI 0.70–2.33). The risk was not higher up to age 5 years, or after age 10 years. In combined analyses, there was no overall increased risk after ICSI. When stratifying by sex, a higher risk was seen after ICSI for boys (aHR 1.69, 95% CI 1.18–2.42), but not for girls (aHR 0.65, 95% CI 0.37–1.16). The combined risk after cryopreservation (aHR 1.42, 95% CI 0.95–2.13) was driven by a higher risk in boys (aHR 1.79, 95% CI 1.09–2.94), while no evidence of an association was found in girls (aHR 1.01, 95% CI 0.50–2.03). No increased risk was seen with IVF or after fresh transfer for either boys or girls.

LIMITATIONS, REASONS FOR CAUTION: Childhood cancer is a rare outcome, and some analyses of cancer subtypes were likely underpowered.

WIDER IMPLICATIONS OF THE FINDINGS: Results from this large registry-based study suggest that addressing age- and sex-specific differences in the risk of childhood cancer following ART conception reveals increased risks for certain groups. Our findings require further study with consideration of possible underlying sex-specific mechanisms related to ART and different childhood cancers.

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Introduction

ART, which includes IVF and ICSI, is a medical treatment offered to couples who have difficulty conceiving naturally. To date, more than 10 million ART-conceived children have been born (De Geyter et al., 2020; Adamson et al., 2023). ART techniques, which include the pharmacological stimulation of ovarian follicles, oocyte retrieval and sperm preparation, and culture and cryopreservation of embryos, differ substantially from natural conception. Concerns have been raised regarding the potential long-term health risks of children conceived through ART (Chen and Heilbronn, 2017; Berntsen et al., 2019; Sciorio et al., 2023). In particular, the relationship between ART and risk of childhood cancer has shown diverse outcomes in prior research (Hargreave et al., 2013, 2019; Lerner-Geva et al., 2017; Williams et al., 2018; Spector et al., 2019; Sargisian et al., 2022; Weng et al., 2022), and whether children born after ART are at increased risk of childhood cancer remains unclear.

Several studies worldwide of children born after ART have reported no overall increased risk of cancer for children conceived after ART (Raimondi et al., 2005; Sundh et al., 2014; Gilboa et al., 2019; Hargreave et al., 2019; Spaan et al., 2019; Spector et al., 2019). However, childhood cancers originate in different tissues with different aetiologies. Multiple studies have indicated a heightened risk of specific types of childhood cancers following ART. Several studies have found a higher rate of hepatic tumours among children conceived through ART (Hargreave et al., 2013; Williams et al., 2013, 2018; Spector et al., 2019; Weng et al., 2022). Also, the risks of central nervous system (CNS) tumours (Sundh et al., 2014), including neuroblastomas (Hargreave et al., 2013), and the risks of retinoblastomas (Hargreave et al., 2013; Lerner-Geva et al., 2017) and leukaemia (Reigstad et al., 2016; Weng et al., 2022) have been found to be higher in children conceived with ART. Similarly, malignant epithelial neoplasms (Sundh et al., 2014), including melanoma (Sargisian et al., 2022), have also been shown to be more frequent in children conceived with ART. There is a higher incidence of childhood cancers in boys compared to girls, and several of the subtypes above are more frequent in boys (Steliarova-Foucher et al., 2017b). Still, studies examining whether there are sex differences in cancer risk after ART conception are lacking. We identified only one previous study that assessed cancer risk after mode of conception and stratified estimates by sex, with the authors concluding there was no evidence that risk differed by child sex (Weng et al., 2022).

Some subtypes of childhood cancer risk are more commonly diagnosed in certain age periods during childhood. While solid and liquid malignancies are the most common in the youngest age group (0–5 years), and solid tumours again are the most common tumour in age 10–18 years, the CNS tumours are slightly more commonly diagnosed in the age group 5–10 years (Stensvold and Dahlen, 2024).

Risk of childhood cancer may also vary by ART treatment modality. In particular, previous studies have suggested that conceptions that include the transfer of cryopreserved embryos (Sargisian et al., 2022) or fertilization by ICSI (Spaan et al., 2019) may be associated with higher cancer risks than fresh embryo transfers or IVF without ICSI. However, whether there are any

sex-specific risks with these different modalities has not yet been investigated.

While the biological mechanisms underlying associations between ART and cancer risk are unclear, an epigenetic study of ART offspring found 10 differentially methylated CpGs within the bidirectional promoter of *BRCA1* in children conceived with ART (Håberg et al., 2022). *BRCA1* is involved in cell division and plays an important role in genome maintenance and gene expression (Tarsounas and Sung, 2020). *BRCA1* is established as a risk gene for several cancers in adult age, but alterations in *BRCA1* function may also influence risk of cancer in younger ages (Ford et al., 1994). The risk of cancer with genetic alteration of *BRCA1* is higher among females compared to males, and *BRCA1*-related cancers in females have an earlier average age of diagnosis compared to *BRCA1*-related cancers in males (Thompson and Easton, 2002; Tai et al., 2007).

Leveraging over 39 years of data from high-quality and comprehensive Norwegian registries, the aim of this study was to evaluate whether risk of childhood cancer in children conceived with ART differed by sex and age, and whether there were sex differences in risk of cancer by ART treatment method and childhood cancer type.

Materials and methods

Records of all registered births in Norway between 1 January 1984 (the year of the first ART conception in Norway) and 31 December 2022 were extracted from the Medical Birth Registry of Norway (MBRN). Birth records were linked with the Cancer Registry of Norway and the Population Register using the unique person ID number allocated to all Norwegian citizens. We extracted cancer diagnoses to 31 December 2023. Further information on data sources is presented in [Supplementary Table S1](#).

The established definition of ART includes only assisted conception methods which involve the manual handling of oocytes and sperm, or embryo outside the body (Zegers-Hochschild et al., 2009). We therefore defined ART as only IVF or ICSI. The non-ART (non-IVF/ICSI) group contains births conceived by intrauterine insemination and ovulation induction. Births conceived by IVF/ICSI were to couples or single women with a diagnosis of infertility, and could include treatments with donor sperm. IVF/ICSI for preimplantation diagnosis was also included, but in a very small number (<0.1% of the IVF/ICSI cases). All clinics which provide ART treatment in Norway are mandated to notify the MBRN of any pregnancy resulting from ART. Information on whether the pregnancy was conceived by ART is also recorded on the birth notification form completed by midwives. These two sources of information within the MBRN were used to ascertain whether the birth resulted from ART conception.

All cancer diagnoses in the cancer registry are coded according to topography (site), morphology, and tumour behaviour using the International Classification of Diseases for Oncology Third Edition (ICD-0-3). To reflect the importance of morphology rather than site for cancers in childhood, all diagnoses were converted to the International Classification of Childhood Cancer Third Edition (ICCC-3) (Steliarova-Foucher et al., 2017a) using

ICD-0-3 codes. We defined childhood cancer as the presence of at least one ICC-3 diagnosis before the age of 18 years.

Statistical analyses

We used Cox proportional hazards regression to estimate the association between ART conception and childhood cancer, for boys and girls combined and also stratified by sex and age group. The time metric was attained age, with time at risk beginning at birth and ending at first cancer diagnosis, 18th birthday or 31 December 2023, whichever came first. Children were censored at death not due to cancer or emigration until December 2022, while these data were not available for 2023. The main outcome was any diagnosis of childhood cancer by attained age (<18 years; <5 years, 5 to <10 years, 10 to <18 years). The risk of childhood cancer was also assessed according to whether the specific ART method used was IVF only or ICSI, and whether the embryo transferred was fresh or cryopreserved-thawed. To take into account secular trends in ART methods, we conducted sensitivity analyses restricted to births from 2000 onwards to reflect the increasing use of ART over the last 25 years. Using the first diagnosis of cancer by ICC-3 group, we also conducted childhood cancer-type specific analyses for subtypes with at least five children in the ART group.

All analyses were adjusted for birth year, maternal age, paternal age, parity, multiple birth, and parental history of cancer. Due to the possibility that multiple birth may operate as a mediator as well as potential confounder of the association under study, we also conducted a sensitivity analysis without adjustment for multiple birth. We used robust standard errors to account for dependency between siblings. In sensitivity analyses, we calculated effect estimates and bias-corrected confidence intervals based on statistics from 200 bootstrap samples using resampling without replacement (Efron and Tibshirani, 1986). The bootstrap method is highly effective for approximating the sampling distribution of statistics, especially for small sample sizes such as those observed for subtypes of childhood cancer in this analysis (Efron and Tibshirani, 1986; Stine, 1989). The validity of the proportional hazards assumption was assessed using Schoenfeld residuals, and there was no evidence of violation. Plots of scaled Schoenfeld residuals against time are presented in [Supplementary Fig. S1](#). As the percentage of missing data was extremely low, no imputation was done for missing data. All analyses were performed using Stata version 17.

Ethical approval

This study was approved by the Norwegian Regional Committee for Medicine and Health Research Ethics (No. 282989) which provided a waiver of consent for participants.

Results

Overall childhood cancer

There were 2 255 025 eligible children born between 1 January 1984 and 31 December 2022, of whom 2.4% ($n = 53\ 694$) were conceived by ART (IVF/ICSI) ([Supplementary Fig. S2](#)). The mean length of follow-up was 13.7 years (SD 5.8).

The mothers of children who were conceived via ART were more likely to be primiparous and older, and less likely to report smoking in pregnancy ([Table 1](#), data not shown). While the birth years for children not conceived via ART were evenly distributed across birth years, children conceived by ART were concentrated in more recent birth years with 88% ($n = 47\ 218$) recorded from 2000 onwards. Compared to children not conceived via ART,

those conceived via ART were more likely to be low birthweight, born preterm, and to be part of a multiple birth ([Table 1](#)).

Among the total study population, 5620 (0.25%) children had a record of at least one ICC-3 diagnosis in the cancer registry before their 18th birthday. Of these 5620 children, 74 had more than one cancer diagnosis. Among ART-conceived children, there were 126 (0.23%) children with cancer, and among children not conceived via ART, there were 5494 (0.25%) with cancer. The cumulative incidence of childhood cancer among all children was higher in those conceived by ART compared to non-ART-conceived children (21.5 per 100 000 person-years for ART-conceived, 17.5 per 100 000 person-years for non-ART conceived; log-rank $P = 0.04$; [Fig. 1A](#)). When combining both sexes, all cancers, and all ages from birth to age 18 years, there was no strong evidence of an overall increased risk in adjusted analysis (adjusted hazard ratio (aHR) 1.13, 95% CI 0.94, 1.36 based on 126 cases among ART-conceived children; [Table 2](#)).

Sex- and age-stratified cancer risk

A trend towards a higher cumulative incidence of childhood cancer in ART-conceived children was seen in boys but there was no clear indication of increased incidence in girls ($P_{\text{boys}} = 0.04$, $P_{\text{girls}} = 0.39$; [Fig. 1A](#)). When combining all ages and all cancers, there was no clear evidence of an overall association between ART conception and childhood cancer before age 18 years in either boys or girls (aHR for boys 1.22, 95% CI 0.95, 1.57, based on 71 cases among ART-conceived boys; aHR for girls 1.03, 95% CI 0.78, 1.37, based on 55 cases among ART-conceived girls; [Table 2](#)). There was little evidence of increased risk of childhood cancer following ART in the youngest (0 to <5 years) or oldest (10 to <18 years) age groups. However, among children aged 5–9 years there was evidence of an increased risk of cancer in ART-conceived boys (aHR 1.73, 95% CI 1.09, 2.74, based on 22 cases among ART-conceived boys), but no strong evidence of increased risk among ART-conceived girls (aHR 1.28, 95% CI 0.70, 2.33, based on 13 cases among ART-conceived girls).

Childhood cancer and ART method

Among children conceived by ART, just over half (53.7%, $n = 28\ 851$) were conceived by IVF, one-third by ICSI (34.6%, $n = 18\ 588$), and the remainder were registered with either unknown or a combination of methods (11.7%, $n = 6255$) ([Supplementary Table S2](#)).

When analysing girls and boys up to age 18 years together, there was no strong evidence that either IVF or ICSI were associated with a higher risk of childhood cancer (IVF aHR 1.18, 95% CI 0.93, 1.49, based on 74 cases among IVF-conceived; ICSI aHR 1.18, 95% CI 0.87, 1.59, based on 44 cases among ICSI-conceived; [Fig. 1C](#), [Table 3](#)). However, when stratifying by sex, boys conceived via ICSI had a higher risk of childhood cancer compared to boys not conceived via ART (aHR 1.69, 95% CI 1.18, 2.42, based on 32 cases among ICSI-conceived boys), while no increased risk was seen in girls conceived by ICSI (aHR 0.65, 95% CI 0.37, 1.16, based on 12 cases among ICSI-conceived girls). With IVF, no clear increased risk of cancer was seen in boys or girls (aHR 1.07, 95% CI 0.77, 1.51, based on 36 IVF-conceived boys; aHR 1.29, 95% CI 0.93, 1.80, based on 38 IVF-conceived girls; [Table 3](#)).

There was some (not significant) evidence that conception following the transfer of cryopreserved embryos was associated with a higher risk of childhood cancer before age 18 years (aHR 1.42, 95% CI 0.95, 2.13, based on 24 cases among those conceived via the use of cryopreserved embryo) but the risk was not increased following fresh embryo transfer (aHR 1.15, 95% CI 0.93, 1.43, based on 92 cases among children conceived via fresh

Table 1. Characteristics of children born 1984–2022 in Norway (n = 2 255 025).

	Children born 1984–2022					
	All (N = 2 255 025)		ART-conceived (IVF/ICSI) (N = 53 694)		Non-ART conceived (N = 2 201 331)	
	n	(%)	n	(%)	n	(%)
Year of birth						
1984–1993	564 908	(25.1)	2099	(3.9)	562 809	(25.6)
1994–2003	585 574	(26.0)	9278	(17.3)	576 296	(26.2)
2004–2013	597 850	(26.5)	18 288	(34.1)	579 562	(26.3)
2014–2022	506 693	(22.5)	24 029	(44.8)	482 664	(21.9)
Sex						
Male	1 158 443	(51.4)	27 666	(51.5)	1 130 777	(51.4)
Female	1 096 582	(48.6)	26 028	(48.5)	1 070 554	(48.6)
Gestation length^a						
Mean (days) (SD)	279 (14.6)		271 (19.8)		279 (14.4)	
<37 weeks	139 252	(6.2)	8924	(16.6)	130 328	(5.9)
≥37 weeks	2 032 898	(90.1)	42 500	(79.2)	1 990 398	(90.4)
Birthweight^b						
Mean (SD)	3512 (597)		3232 (750)		3519 (591)	
<2500 g	105 126	(4.7)	7934	(14.8)	97 192	(4.4)
≥2500 g	2 148 347	(95.3)	45 730	(85.2)	2 102 617	(95.5)
Multiplicity						
Singleton	2 186 175	(96.9)	41 872	(78.0)	2 144 303	(97.4)
Twin/higher order multiple	68 850	(3.1)	11 822	(22.0)	41 872	(1.9)
Maternal parity						
Primiparous	946 894	(42.0)	33 627	(62.6)	913 267	(41.5)
Multiparous	1 308 131	(58.0)	20 067	(37.4)	1 288 064	(58.5)
Maternal age at birth						
Mean (SD)	29.1 (5.2)		33.5 (4.35)		29.0 (5.17)	
<24	439 997	(19.5)	762	(1.4)	439 235	(20.0)
25–29	767 541	(34.0)	9268	(17.3)	758 273	(34.4)
30–34	695 531	(30.8)	22 018	(41.0)	673 513	(30.6)
35–39	296 702	(13.2)	17 362	(32.3)	279 340	(12.7)
≥40	55 254	(2.5)	4284	(8.0)	50 970	(2.3)

Note: presented as mean (SD) or count (percentages).

^a Missing data on gestation length n = 82 875.

^b Missing data on birthweight n = 1552.

embryo transfer; Fig. 1B, Table 3). Compared to boys not conceived via ART, the use of cryopreserved embryos was associated with an increased cancer risk (aHR 1.79, 95% CI 1.09, 2.94, based on 16 cases among boys conceived via cryopreserved embryos), but there was no strong evidence of an increased risk for boys conceived by fresh embryo transfer (Table 3). Among girls, neither fresh embryo transfer nor the use of cryopreserved embryos were associated with the risk of childhood cancer (Table 3).

Estimates for the association between ART method and childhood cancer <18 years restricting to births after the year 2000 were similar to the estimates derived using the full sample (Supplementary Table S3). Adjusted estimates were also very similar regardless of whether multiple birth was adjusted for or not (Supplementary Table S4).

Bootstrap-estimated HRs and bias-corrected confidence intervals are presented in Supplementary Tables S5 and S6. Bootstrap estimates were very similar in both magnitude, directionality, and significance to the main estimates, supporting validity of the results obtained from Cox models.

Risk of childhood cancer by cancer type

Additional analyses were carried out by childhood cancer types where there were more than five cases in the ART group (Supplementary Table S7). For leukaemia (ICCC-3 group 1), there was an increased risk following ART conception among boys (aHR 1.60, 95% CI 1.04, 2.46, based on 23 cases among ART-conceived boys), but no evidence of an increased risk among girls. For lymphomas (ICCC-3 group II), there was a trend towards increased risk of childhood cancer before age 18 years, with similar

estimates observed for boys and girls, though the evidence was not strong (aHR for boys 1.55, 95% CI 0.80, 3.01, based on 10 cases in ART-conceived boys; aHR for girls 1.65, 95% CI 0.77, 3.56, based on seven cases in ART-conceived girls). There was no evidence of an increased risk of cancer following ART conception for the following childhood cancer subtypes: AML, ALL, CNS tumours (group III), and neuroblastoma and other peripheral nervous cell tumours (group IV). For both renal tumours (ICCC-3 group VI) and soft tissue sarcomas (group IX), the aHR was suggestive of an increased risk for boys, though there was no clear evidence and numbers were small (aHR for renal tumours in boys 2.34, 9% CI 0.86, 6.38; aHR for soft tissue sarcomas in boys 2.16, 95% CI 0.93, 5.02; case numbers among ART-conceived children cannot be reported by sex for privacy reasons). The sample size was too small to carry out estimations among girls. There were insufficient cases to look at the following childhood cancer subtypes: retinoblastoma (group V), hepatic tumours (group VII), bone tumours (group VIII), germ cell and gonadal tumours (group X), epithelial tumours and melanoma (group XI), or other and unspecified tumours (group XII).

Discussion

Using Norwegian registry data on over 2 million infants born between 1984 and 2020, we found that stratifying on age and sex is important when studying cancer risk in children conceived with ART. There was evidence of an increased risk of being diagnosed with childhood cancer following ART conception between 5 and 9 years, especially in boys. A higher risk of cancer was seen

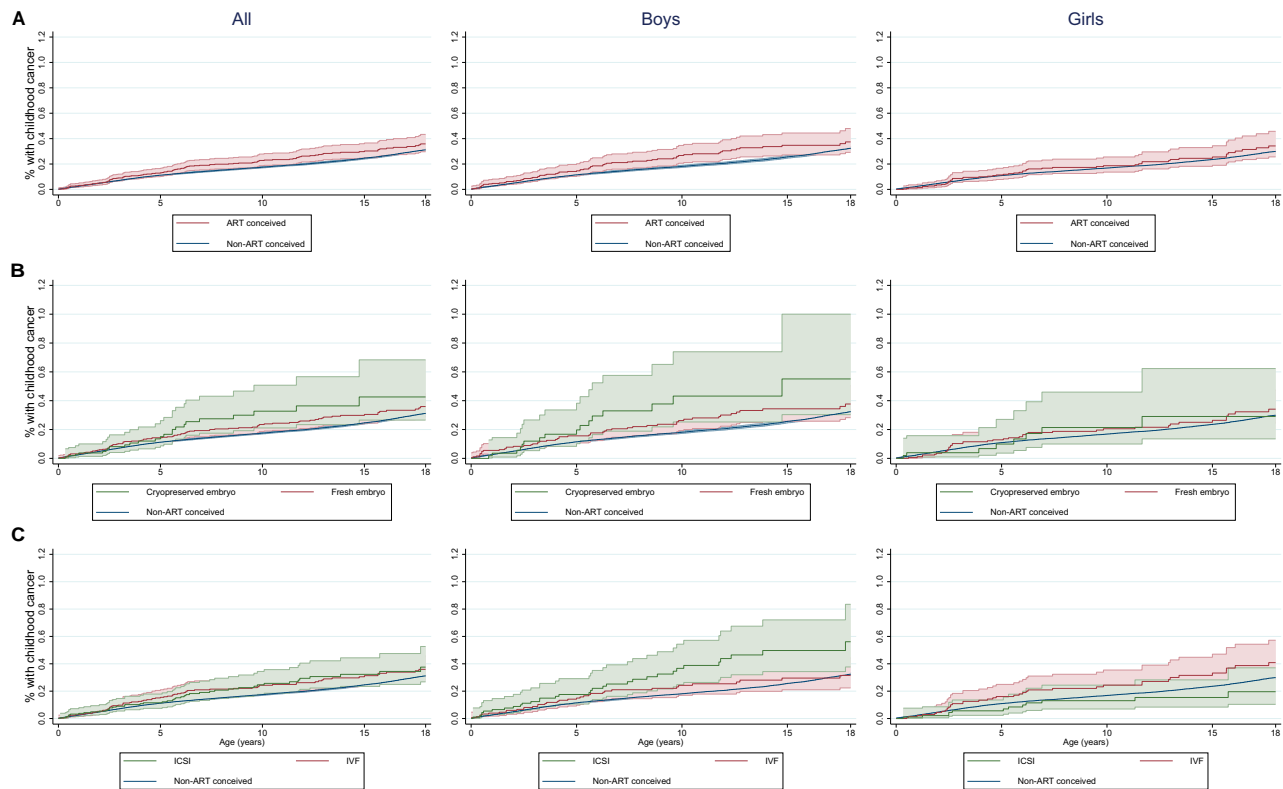


Figure 1. Overall and sex-stratified cumulative incidence curves for childhood cancer. (A) Any ART conception, (B) fresh versus cryopreserved embryos, (C) ICSI versus IVF. P-values for log-rank tests: any ART/non-ART: $P=0.04$ (all children), $P=0.04$ (boys), $P=0.39$ (girls); cryopreserved/fresh/non-ART: $P=0.02$ (all children), $P=0.008$ (boys), $P=0.60$ (girls); IVF/ICSI/non-ART: $P=0.05$ (all children), $P=0.002$ (boys), $P=0.06$ (girls).

among boys of any age conceived via ICSI, while this was not seen in girls. The higher risk seen among all children after cryopreservation was driven by a higher risk in boys, while there was no strong evidence of association among girls.

A number of previous studies have investigated the association between ART conception and childhood cancer, with conflicting findings (Raimondi *et al.*, 2005; Sundh *et al.*, 2014; Reigstad *et al.*, 2016; Spaan *et al.*, 2019; Spector *et al.*, 2019; Sargisian *et al.*, 2022; Weng *et al.*, 2022). The present study includes more than twice as many ART-conceived children as the most recently previously published analysis of Norwegian data, with an additional 12 years of follow-up (Reigstad *et al.*, 2016). Although childhood cancers include various cancer type with different aetiologies, and differ with age and sex, studies investigating the age- or sex-stratified risk of childhood cancer following ART conception have been lacking.

Our results suggest that the risk of childhood cancer in offspring following ART may vary by offspring sex and age. Therefore, it would be prudent for future studies to avoid combining both sexes, all cancer types, and all childhood ages together when investigating the risk of childhood cancer after ART. While there was no overall association between ART conception and childhood cancer before age 18 years in either boys or girls, stratification by age revealed noteworthy patterns. Among children aged 5–9 years, there was evidence of an increased risk of cancer, especially in ART-conceived boys. It was unclear what type of cancer drove the higher risk in this age group. For girls in this age group, although not statistically significant, there was a trend towards an increased risk at age 5–9 years. These findings underscore the importance of considering age-specific risks when assessing the impact of ART conception on childhood cancer.

We also found that there were sex-specific risks of childhood cancer according to whether IVF or ICSI was used as the method for fertilizing the oocyte, and whether the embryo was cryopreserved before embryo transfer. In Norway, the main indication for ICSI is male factor infertility, and ICSI is not commonly used for other indications such as total fertilization failure by IVF. Therefore, the specific increased cancer risk with ICSI could be potentially explained by factors associated with male factor infertility (the predominant underlying indication for ICSI), rather than mechanisms associated with ART use itself. However, as we also see differences with cryopreserved embryos, underlying uniparental subfertility is unlikely to be the only explanation for an increase in cancer risk in children conceived by ART. Disentangling the impact of ART treatment from the potential impact of the underlying parental cause of infertility is challenging, and this analysis was limited by an inability to take into account the indication for ART.

Additionally, the use of cryopreserved-thawed embryos was associated with a higher risk of childhood cancer compared to fresh embryo transfer. Trends over time show a shift towards more cycles performed by the use of cryopreserved embryos (Smeenk *et al.*, 2023), and more studies clarifying a potential cancer risk with this method are warranted. However, the maternal risk of hypertensive disorders of pregnancy is higher following the use of cryopreserved embryos, as is the risk of having a large-for-gestational-age or higher birth weight baby (Zaat *et al.*, 2021). Since higher birth weight is associated with childhood cancers including leukaemias, CNS tumours, and renal tumours (O'Neill *et al.*, 2015), this may partly explain some of our findings.

One potential mechanism associated with ART and cancer is epigenetic changes (Chen and Heilbronn, 2017). Epigenetic

Table 2. Overall and sex-stratified association between ART conception (IVF/ICSI) and childhood cancer by age group.

Age	All children						Boys			Girls		
	No. of cases	Hazard ratio (95% CI)		No. of cases	Hazard ratio (95% CI)		No. of cases	Hazard ratio (95% CI)		No. of cases	Hazard ratio (95% CI)	
		Unadjusted	Adjusted ^a		Unadjusted	Adjusted ^a		Unadjusted	Adjusted ^a		Unadjusted	Adjusted ^a
0 to <18 years	ALL	5620	ref	3001	ref	2619	ref	ref	2564	ref	ref	ref
	Non-ART	5494	ref	2930	ref	2564	ref	ref	2564	ref	ref	ref
	ART (IVF/ICSI)	126	1.20 (1.01, 1.44)	71	1.13 (0.94, 1.36)	55	1.27 (1.01, 1.61)	1.22 (0.95, 1.57)	1.12 (0.86, 1.47)	1.03 (0.78, 1.37)		
0 to <5 years	ALL	2433	ref	1283	ref	1150	ref	ref	1123	ref	ref	ref
	Non-ART	2369	ref	1246	ref	1123	ref	ref	1123	ref	ref	ref
	ART (IVF/ICSI)	64	1.17 (0.91, 1.50)	37	1.09 (0.84, 1.42)	27	1.28 (0.92, 1.77)	1.23 (0.87, 1.74)	1.04 (0.71, 1.53)	0.95 (0.64, 1.41)		
≥5 to <10 years	ALL	1190	ref	649	ref	541	ref	ref	528	ref	ref	ref
	Non-ART	1155	ref	627	ref	528	ref	ref	528	ref	ref	ref
	ART (IVF/ICSI)	35	1.59 (1.13, 2.22)	22	1.53 (1.06, 2.20)	13	1.84 (1.20, 2.81)	1.73 (1.09, 2.74)	1.29 (0.74, 2.23)	1.28 (0.70, 2.33)		
≥10 to <18 years	ALL	1997	ref	1069	ref	928	ref	ref	913	ref	ref	ref
	Non-ART	1970	ref	1057	ref	913	ref	ref	913	ref	ref	ref
	ART (IVF/ICSI)	27	0.97 (0.67, 1.42)	12	0.91 (0.61, 1.34)	15	0.81 (0.46, 1.43)	0.79 (0.43, 1.44)	1.16 (0.70, 1.94)	1.02 (0.61, 1.71)		

^a Adjusted for birth year, maternal age, paternal age, multiple births, parity, and parental history of cancer. The reference level corresponds to non-ART. Bold font indicates statistical significance ($P < 0.05$).

Table 3. Overall and sex-stratified association between ART conception (IVF/ICSI) and childhood cancer by ART method.

ART method	All children			Boys			Girls		
	No. of cases	Hazard ratio		No. of cases	Hazard ratio		No. of cases	Hazard ratio	
		Unadjusted	(95% CI) Adjusted ^a		Unadjusted	(95% CI) Adjusted ^a		Unadjusted	(95% CI) Adjusted ^a
Non-ART	5494	ref	ref	2930	ref	ref	2564	ref	ref
IVF	74	1.23 (0.98, 1.55)	1.18 (0.93, 1.49)	36	1.10 (0.79, 1.52)	1.07 (0.77, 1.51)	38	1.39 (1.01, 1.92)	1.29 (0.93, 1.80)
ICSI	44	1.28 (0.95, 1.72)	1.18 (0.87, 1.59)	32	1.82 (1.29, 2.58)	1.69 (1.18, 2.42)	12	0.72 (0.41, 1.26)	0.65 (0.37, 1.16)
Embryo type	5494	ref	ref	2930	ref	ref	2564	ref	ref
Fresh embryo	92	1.22 (0.99, 1.50)	1.15 (0.93, 1.43)	51	1.27 (0.96, 1.67)	1.22 (0.91, 1.63)	41	1.16 (0.85, 1.58)	1.08 (0.78, 1.48)
Cryopreserved embryo	24	1.55 (1.04, 2.32)	1.42 (0.95, 2.13)	16	1.92 (1.17, 3.14)	1.79 (1.09, 2.94)	8	1.12 (0.56, 2.24)	1.01 (0.50, 2.03)

^a Adjusted for birth year, maternal age, paternal age, multiple births, parity, and parental history of cancer. The reference level corresponds to non-ART. Bold font indicates statistical significance ($P < 0.05$).

differences with ART conceptions have been found to mediate difference in birthweight associated with different ART methods (Carlsen et al., 2022). It is currently uncertain how epigenetic findings in children conceived with ART specifically relate to future cancer outcomes for both boys and girls. Further research incorporating long-term follow-up is needed to investigate the long-term clinical significance of these epigenetic modifications in terms of cancer risk in both sexes.

Strengths and limitations

This analysis is based on 39 years of high-quality Nordic registry data, including all live-born children born between 1984 and 2022. The Cancer Registry of Norway is regarded as having close-to-complete data on cancer diagnoses in Norway, with overall completeness estimated at 98.8% for the period 2001–2005 (Larsen et al., 2009). Cancer diagnoses in childhood were classified according to ICCC-3 to enable comparability with previous studies. All clinics in Norway providing ART are required by law to report pregnancies conceived by ART to the MBRN, and this information is supplemented by a question about ART conception on the birth notification form. Information was not available for the indication for ART use during the whole study period, and it is possible that in a very small number of cases, the indication for ART use was for reasons other than subfertility, e.g. preimplantation genetic diagnosis.

Although we included all births from the year of the first ART birth in Norway, there were very few births following ART in the early years: 4% of ART births in our analysis occurred between 1984 and 1993 compared to 45% between 2014 and 2022. ART practices have changed immeasurably over this time period. To account for this, we adjusted for birth year and additionally conducted sensitivity analyses restricting to births from 2000 onwards, when both ICSI and the use of cryopreserved embryos were more prevalent.

Despite the large overall sample size, we were likely underpowered to look at age-specific risks and the risk associated with different ART methods (IVF vs ICSI, cryopreserved vs fresh embryo). Despite our overall finding of no significantly increased risk in either boys or girls, virtually all of the aHRs were suggestive of an increased risk (>1.00). Previous studies have found associations between ART conception and specific subtypes of childhood cancer such as hepatic cancer (Hargreave et al., 2013; Williams et al., 2013, 2018; Spector et al., 2019; Weng et al., 2022), neuroblastoma (Hargreave et al., 2013), and retinoblastoma (Hargreave et al., 2013; Lerner-Geva et al., 2017), however, due to limited numbers in our study, we were generally unable to address associations for these rare subtypes.

We did not adjust for maternal smoking or BMI, as this information was not collected in the birth registry in earlier years. However, MBRN data from later years show that women conceiving via ART are less likely to smoke and did not significantly differ in BMI compared to the fertile population (Magnus et al., 2021). Additionally, we did not have access to information on parental socioeconomic status. Although socioeconomic status is generally associated with ART use, the association is likely weaker in the Norwegian setting where most ART treatment is publicly funded. Additionally, there is scant evidence of a strong association with offspring risk of childhood cancer (Kehm et al., 2018). We can thus assume any unmeasured confounding present would be unlikely to bias the true association.

Conclusion

In conclusion, we did not observe strong evidence for an overall association between ART conception and childhood cancer before age 18 years in either boys or girls. However, the risk of being diagnosed with cancer between ages 5–9 years was increased in children conceived with ART, especially in boys. Conception via ICSI or following the use of cryopreserved embryos was associated with a higher risk of childhood cancer in boys. Additionally, there was evidence of an increased risk of leukaemia in ART-conceived boys. Our findings suggest that there may be sex differences in the impact of ART conception on childhood cancer risk driven by specific ART method. However, further research is needed, particularly given the continuing increase in the use of ICSI in cases without male factor infertility.

Supplementary data

Supplementary data are available at *Human Reproduction* online.

Data availability

Study data are available on application via helsedata.no, subject to the necessary ethics approvals.

Authors' roles

All authors agree to be accountable for all aspects of the work. Study concept and design: L.L.O., D.K., M.C.M.-K., H.N.T., Y.L., H.I.H., L.B.R., R.L., and S.E.H. Obtained funding: S.E.H., R.L. Acquisition of data: S.E.H. Analysis of data: L.L.O. and H.N.T. Interpretation of data: L.L.O., D.K., M.C.M.-K., H.N.T., Y.L., H.I.H., L.B.R., R.L., and S.E.H. Drafting the manuscript: L.L.O., D.K., and S.E.H. Critical revision of the manuscript for important intellectual content: M.C.M.-K., H.N.T., Y.L., H.I.H., L.B.R., and R.L. Final approval of the manuscript: L.L.O., D.K., M.C.M.-K., H.N.T., Y.L., H.I.H., L.B.R., R.L., and S.E.H. Study supervision: S.E.H.

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Conflict of interest

The authors declare no conflict of interests.

References

- Adamson GD, Dyer S, Zegers-Hochschild F, Chambers G, De Mouzon J, Ishihara O, Kupka M, Baker V, Banker M, Elgindy E et al. O-154 ICMART preliminary world report 2019. *Hum Reprod* 2023; **38**:dead093.187.
- Berntsen S, Söderström-Anttila V, Wennerholm U-B, Laivuori H, Loft A, Oldereid NB, Romundstad LB, Bergh C, Pinborg A. The health of children conceived by ART: 'the chicken or the egg'? *Hum Reprod Update* 2019; **25**:137–158.
- Carlsen EØ, Lee Y, Magnus P, Jugessur A, Page CM, Nustad HE, Håberg SE, Lie RT, Magnus MC. An examination of mediation by

- DNA methylation on birthweight differences induced by assisted reproductive technologies. *Clin Epigenetics* 2022;**14**:151.
- Chen M, Heilbronn L. The health outcomes of human offspring conceived by assisted reproductive technologies (ART). *J Dev Orig Health Dis* 2017;**8**:388–402.
- De Geyter C, Calhaz-Jorge C, Kupka MS, Wyns C, Mocanu E, Motrenko T, Scaravelli G, Smeenk J, Vidakovic S, Goossens V; European IVF-monitoring Consortium (EIM) for the European Society of Human Reproduction and Embryology (ESHRE). ART in Europe, 2015: results generated from European registries by ESHRE. *Hum Reprod Open* 2020;**2020**:hoaa038.
- Efron B, Tibshirani R. Bootstrap methods for standard errors, confidence intervals, and other measures of statistical accuracy. *Stat Sci* 1986;**1**:54–75.
- Ford D, Easton DF, Bishop DT, Narod SA, Goldgar DE. Risks of cancer in BRCA1-mutation carriers. *Lancet* 1994;**343**:692–695.
- Gilboa D, Koren G, Barer Y, Katz R, Rotem R, Lunenfeld E, Shalev V. Assisted reproductive technology and the risk of pediatric cancer: a population based study and a systematic review and meta analysis. *Cancer Epidemiol* 2019;**63**:101613.
- Håberg SE, Page CM, Lee Y, Nustad HE, Magnus MC, Haftorn KL, Carlsen EØ, Denault WRP, Bohlin J, Jugessur A et al. DNA methylation in newborns conceived by assisted reproductive technology. *Nat Commun* 2022;**13**:1896.
- Hargreave M, Jensen A, Hansen MK, Dehlendorff C, Winther JF, Schmiegelow K, Kjær SK. Association between fertility treatment and cancer risk in children. *Jama* 2019;**322**:2203–2210.
- Hargreave M, Jensen A, Toender A, Andersen KK, Kjaer SK. Fertility treatment and childhood cancer risk: a systematic meta-analysis. *Fertil Steril* 2013;**100**:150–161.
- Kehm RD, Spector LG, Poynter JN, Vock DM, Osypuk TL. Socioeconomic status and childhood cancer incidence: a population-based multilevel analysis. *Am J Epidemiol* 2018;**187**:982–991.
- Larsen IK, Småstuen M, Johannesen TB, Langmark F, Parkin DM, Bray F, Møller B. Data quality at the Cancer Registry of Norway: an overview of comparability, completeness, validity and timeliness. *Eur J Cancer* 2009;**45**:1218–1231.
- Lerner-Geva L, Boyko V, Ehrlich S, Mashiach S, Hourvitz A, Haas J, Margalioth E, Levran D, Calderon I, Orvieto R et al. Possible risk for cancer among children born following assisted reproductive technology in Israel. *Pediatr Blood Cancer* 2017;**64**:e26292.
- Magnus MC, Wilcox AJ, Fadum EA, Gjessing HK, Opdahl S, Juliusson PB, Romundstad LB, Håberg SE. Growth in children conceived by ART. *Hum Reprod* 2021;**36**:1074–1082.
- O'Neill KA, Murphy MF, Bunch KJ, Puumala SE, Carozza SE, Chow EJ, Mueller BA, McLaughlin CC, Reynolds P, Vincent TJ et al. Infant birthweight and risk of childhood cancer: international population-based case control studies of 40 000 cases. *Int J Epidemiol* 2015;**44**:153–168.
- Raimondi S, Pedotti P, Taioli E. Meta-analysis of cancer incidence in children born after assisted reproductive technologies. *Br J Cancer* 2005;**93**:1053–1056.
- Reigstad MM, Larsen IK, Myklebust TÅ, Robsahm TE, Oldereid NB, Brinton LA, Storeng R. Risk of cancer in children conceived by assisted reproductive technology. *Pediatrics* 2016;**137**:e20152061.
- Sargisian N, Lantering B, Petzold M, Opdahl S, Gissler M, Pinborg A, Henningsen A-KA, Tiitinen A, Romundstad LB, Spangmose AL et al. Cancer in children born after frozen-thawed embryo transfer: a cohort study. *PLoS Med* 2022;**19**:e1004078.
- Sciorio R, Tramontano L, Rapalini E, Bellaminutti S, Bulletti FM, D'Amato A, Manna C, Palagiano A, Bulletti C, Esteves SC. Risk of genetic and epigenetic alteration in children conceived following ART: is it time to return to nature whenever possible? *Clin Genet* 2023;**103**:133–145.
- Smeenk J, Wyns C, De Geyter C, Kupka M, Bergh C, Cuevas Saiz I, De Neubourg D, Rezabek K, Tandler-Schneider A, Rugescu I et al.; European IVF Monitoring Consortium (EIM) for the European Society of Human Reproduction and Embryology (ESHRE). ART in Europe, 2019: results generated from European registries by ESHRE. *Hum Reprod* 2023;**38**:2321–2338.
- Spaan M, van den Belt-Dusebout AW, van den Heuvel-Eibrink MM, Hauptmann M, Lambalk CB, Burger CW, van Leeuwen FE; OMEGA-Steering Group. Risk of cancer in children and young adults conceived by assisted reproductive technology. *Hum Reprod* 2019;**34**:740–750.
- Spector LG, Brown MB, Wantman E, Letterie GS, Toner JP, Doody K, Ginsburg E, Williams M, Koch L, Schymura MJ et al. Association of in vitro fertilization with childhood cancer in the United States. *JAMA Pediatr* 2019;**173**:e190392.
- Steliarova-Foucher E, Colombet M, Ries LAG, Rous B, Stiller CA. ICC Recode Third Edition ICD-O-3/IARC 2017 Table—SEER Recodes, International Classification of Childhood Cancer. USA: Surveillance, Epidemiology, and End Results Program—SEERStat, 2017a.
- Steliarova-Foucher E, Colombet M, Ries LA, Moreno F, Dolya A, Bray F, Hesselting P, Shin HY, Stiller CA, Bouzbid S; IICC-3 Contributors. International incidence of childhood cancer, 2001–10: a population-based registry study. *Lancet Oncol* 2017b;**18**:719–731.
- Stensvold E, Dahlen AH. *Årsrapport (Annual Report) 2023—Resultater og forbedringstiltak fra Nasjonalt kvalitetsregister for barnkreft*. Oslo, Norway: Cancer Registry of Norway, 2024, 3–78.
- Stine R. An introduction to bootstrap methods: examples and ideas. *Sociol Methods Res* 1989;**18**:243–291.
- Sundh KJ, Henningsen A-KA, Källen K, Bergh C, Romundstad LB, Gissler M, Pinborg A, Skjaerven R, Tiitinen A, Vassard D et al. Cancer in children and young adults born after assisted reproductive technology: a Nordic cohort study from the Committee of Nordic ART and Safety (CoNARTaS). *Hum Reprod* 2014;**29**:2050–2057.
- Tai YC, Domchek S, Parmigiani G, Chen S. Breast cancer risk among male BRCA1 and BRCA2 mutation carriers. *J Natl Cancer Inst* 2007;**99**:1811–1814.
- Tarsounas M, Sung P. The antitumorigenic roles of BRCA1–BARD1 in DNA repair and replication. *Nat Rev Mol Cell Biol* 2020;**21**:284–299.
- Thompson D, Easton DF; Breast Cancer Linkage Consortium. Cancer incidence in BRCA1 mutation carriers. *J Natl Cancer Inst* 2002;**94**:1358–1365.
- Weng S-S, Huang Y-T, Huang Y-T, Li Y-P, Chien L-Y. Assisted reproductive technology and risk of childhood cancers. *JAMA Netw Open* 2022;**5**:e2230157.
- Williams C, Bunch K, Murphy M, Stiller C, Botting B, Wallace W, Davies M, Sutcliffe A. Cancer risk in children born after donor ART. *Hum Reprod* 2018;**33**:140–146.
- Williams CL, Bunch KJ, Stiller CA, Murphy MF, Botting BJ, Wallace WH, Davies M, Sutcliffe AG. Cancer risk among children born after assisted conception. *N Engl J Med* 2013;**369**:1819–1827.
- Zaat T, Zagers M, Mol F, Goddijn M, van Wely M, Mastenbroek S; Cochrane Gynaecology and Fertility Group. Fresh versus frozen embryo transfers in assisted reproduction. *Cochrane Database Syst Rev* 2021;**2**:CD011184.
- Zegers-Hochschild F, Adamson GD, de Mouzon J, Ishihara O, Mansour R, Nygren K, Sullivan E, van der Poel S; International Committee for Monitoring Assisted Reproductive Technology; World Health Organization. International Committee for Monitoring Assisted Reproductive Technology (ICMART) and the World Health Organization (WHO) Revised Glossary on ART Terminology, 2009. *Hum Reprod* 2009;**24**:2683–2687.

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