

TITLE: Cancer risk in children born after donor assisted reproductive technology

RUNNING TITLE: Childhood Cancer after donor ART

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ABSTRACT

Study question: Do children born after donor assisted reproductive technology (ART) have an increased risk of developing childhood cancer in comparison to the general population?

Summary answer: There was no overall increased risk of childhood cancer in individuals born after donor ART.

What is known already: Most large population based studies have shown no increase in overall childhood cancer incidence after non-donor ART; however other studies have suggested small increased risks in specific cancer types, including haematological cancers. Cancer risk specifically in children born after donor ART has not been investigated to date.

Study design, size, duration: This retrospective cohort study utilized record linkage to determine outcome status of all 12,186 children born in Great Britain (1992-2008) after donor ART. 12,137 cohort members contributed 95,389 person-years of follow-up (average follow-up 7.86 years).

Participants, setting, methods: Records of all children born in Great Britain (England, Wales, Scotland) after all forms of donor ART (1992-2008) were linked to the UK National Registry of Childhood Tumours (NRCT) to determine the number who subsequently developed cancer by 15 years of age, by the end of 2008. Rates of overall and type specific cancer (selected *a priori*) were compared with age, sex and calendar year standardised population-based rates, stratifying for potential mediating/moderating factors including sex, age at diagnosis, birth weight, multiple births, maternal previous live births, assisted conception type, and fresh/ cryopreserved cycles.

Main results and the role of chance: In our cohort of 12,137 children born after donor assisted reproductive technology (52% male, 55% singleton births), no overall increased risk of cancer was identified. 12 cancers were detected compared to 14.4 expected (Standardised incidence ratio (SIR) 0.83; 95% confidence interval (CI) 0.43-1.45; $P=0.50$). A small, significant increased risk of hepatoblastoma was found, but numbers and absolute risks were small (<5 cases observed; SIR 10.28; 95%CI 1.25-37.14; $P<0.05$). This increased hepatoblastoma risk was associated with low birthweight.

Limitations, reasons for caution: Although this study includes a large number of children born after donor ART, the rarity of specific diagnostic sub-groups of childhood cancer results in few cases and therefore wide confidence intervals for such outcomes. As this is an observational study, it is not possible to adjust for all potential confounders; we have instead used stratification to explore potential moderating and mediating factors, where data are available.

Wider implications of the findings: This study is the first to investigate cancer risk in children born after donor ART. Although based on small numbers, results are reassuring for families and clinicians. The small but significant increased risk of hepatoblastoma detected was associated with low birthweight, a known risk factor for this tumour type. It should be emphasised that absolute risks are very small. However, on-going investigation with longer follow-up is needed.

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Key Words: childhood cancer, assisted reproductive technology, donor treatment, cohort study

INTRODUCTION

Donor ART treatment cycles utilize donor sperm, eggs or embryos and result in approximately 10% of all births after ART in the UK (Human Fertilisation & Emryology Authority 2013). Given that most donors have few, if any, fertility problems, children born after donor ART represent a subtly different population than children born after non-donor ART. This inherent difference, together with increasing use of donor ART cycles and the extra uncertainty faced by couples using donor gametes, places greater importance on follow-up studies differentiating between children born after donor and non-donor ART.

The possibility of an increased risk of childhood cancer in individuals born after ART has been suggested previously (Hargreave et al. 2013; Puumala et al. 2012; Schieve et al. 2004; Sutcliffe and Ludwig 2007; Kallen et al. 2010). Systematic reviews provide conflicting evidence (Raimondi, Pedotti, and Taioli 2005; Hargreave et al. 2013; Reigstad et al. 2017), a recent meta-analysis suggesting a small but significant increased risk of cancer in children born after ART (Relative Risk 1.33; 95%CI 1.08-1.63) (Hargreave et al. 2013). Two large, population based studies, published since, report no overall increased risk and no increased risk in haematological cancers (Sundh et al. 2014; Williams et al. 2013). However, these studies did not include children born after donor ART (Sundh et al. 2014; Williams et al. 2013). A further, smaller, population based study showed no overall increased risk of childhood cancer, but did find a significant increase in leukaemia and Hodgkin lymphoma (Reigstad et al. 2016). This study did include some children born after donor ART but did not estimate risk in this group separately (Reigstad et al. 2016). We conducted a large population-based linkage study, aiming to provide risk estimates for childhood cancer overall and for specific diagnostic subgroups (chosen *a priori*), in individuals born after donor ART.

MATERIALS & METHODS

Population & cohort participants

All records relating to 12,186 children born between 01.01.1992 and 12.31.2008 in Great Britain (England, Wales and Scotland) after donor ART were identified by the Human Fertilization and Embryology Authority (HFEA). Donor ART is defined as ‘all treatments or procedures including in vitro handling of both human oocytes and sperm, or embryos, for the purpose of establishing a pregnancy’ using donor oocytes, sperm or embryos (Zegers-Hochschild et al. 2009). The HFEA is legally required to record treatment and outcome details of all ART cycles in the UK, including those using donor gametes or embryos. Thus the dataset is considered effectively complete (HFEA act 2008).

Ethical approval

Approval for the study was obtained from the National Information Governance Board and the London Research Ethics Committee including approval for the restricted use of data without individual written informed consent. One of the conditions attached to approval of this study prevents the publication of cells containing less than 5 individuals. Patients can withdraw consent for their HFEA data to be used for research. At the time of the study, 0.3% of all families using ART had done so; their data were not included.

Outcome data

Details of cancer incidence were obtained from the National Registry of Childhood Tumours (NRCT). During the study period, the NRCT was the largest national population-based childhood cancer registry world-wide, ascertaining validated information from multiple sources about children under 15 years, diagnosed with cancer in the UK (Kroll et al. 2011). The NRCT is considered almost complete for the study period (Kroll et al. 2011). The International Classification of Childhood Cancer 3rd edition (ICCC3), was used to categorise cancers (Steliarova-Foucher et al. 2005). Co-morbidities, known at the time of a child’s cancer diagnosis, were reported to the NRCT by the registering oncology centre, and data are reasonably complete for major congenital anomalies.

Data linkage

Ethical regulations stipulated that identifiable data were only viewed directly by HFEA staff. Therefore data linkage was undertaken by two members of HFEA staff independently from each other, following a robust data linkage protocol, developed to maximize linkage sensitivity and specificity, used and described in another similar study (Williams et al. 2013). Linkage was directly overseen by CLW, KJB and BB. 12,186 eligible HFEA records of children born after donor ART 1992-2008 were linked to all 14,896 NRCT eligible records of children documented as having been born 1992-2008, and having developed cancer before 01.01.2009. All potential matches using this inclusive linkage protocol were anonymously reviewed by CLW and KJB. BB reviewed any cases where the validity of the match was questionable (n=2, both unanimously rejected by all 3 reviewers).

Statistical analyses and calculation of expected rates

Person-years at risk were calculated from date of birth until the soonest of cancer diagnosis date, December 31, 2008 or child's 15th birthday. 49 children (0.4%) were excluded from analyses as no valid date of birth was available and therefore person-years at risk could not be determined. Expected cancers in the cohort were calculated by multiplying person-years at risk by the corresponding national incidence rates (1-year age bands by calendar year and sex) for children born and diagnosed in Great Britain. Standardized Incidence Ratios (SIR) were calculated comparing observed cancers within the cohort to expected values. 95% confidence intervals and 2-sided P values were calculated assuming a Poisson distribution (Breslow and Day 1987). Analyses were performed using STATA software, version 12 (Stata Corp 2013).

RESULTS

12,137 children contributed 95,389 person-years follow-up, with an average duration of 7.86 years. Cohort demographics are detailed in Table 1.

12 children were linked to NRCT records and therefore identified as having developed cancer. Baseline demographics appear broadly similar for cohort members who did and did not develop cancer (*data not shown separately given small numbers*). The median age at cancer diagnosis was 2.6 years (Inter-quartile range 1.2-5.2). There were no children with more than one cancer diagnosis. 14.4 cancers were expected within the cohort, resulting in an unadjusted SIR of 0.83 (95% CI 0.43-1.45; Table 2). Sensitivity analysis including the two potential cases rejected during data-linkage did not substantially alter results (SIR 0.97; 95% CI 0.53- 1.63; *data not shown*). Results remained non-significant when stratified by sex, age at diagnosis, birthweight, birth multiplicity, maternal parity, type of ART, and fresh vs. cryopreserved embryos (Table 2), although the small number of events in some strata have resulted in wide confidence intervals.

No significant excess risk was seen for any major ICC3 category, with the exception of hepatic tumours (Table 3). A significant excess of hepatic tumours was detected (SIR 9.12; 95%CI 1.11-32.95; Table 3) all of which were hepatoblastomas (SIR 10.28; 95%CI 1.25-37.14; Table 3; Absolute excess risk 18.66 per million person-years at risk, 95%CI 0.24-73.39). This excess was associated with low birthweight and only seen in children with birthweight <2500g (SIR 28.00; 95%CI 3.39-101.14; $P=0.02$; *data not shown*).

DISCUSSION

No overall increased risk of childhood cancer was detected in this large and complete national population based cohort of children born after donor ART. This is in line with two similar recently published cohort studies of children born after non-donor ART (Sundh et al. 2014; Williams et al. 2013). A recently published study combining data on 91,796 children born after non-donor ART in 4

Nordic countries found no significant increase in overall cancer rates (adjusted Hazard Ratio 1.08; 95%CI 0.91-1.27) (Sundh et al. 2014). Similarly our previous study of 106,013 children born after non-donor ART over the same study period and from the same population as our current study, did not show an overall increased risk of cancer (SIR 0.98; 95%CI 0.81-1.19) (Williams et al. 2013).

This study is the first, to our knowledge, to explore cancer risk in children born after donor ART and uses high quality data from two population-based data sets. NRCT data are virtually complete for the study period (Kroll et al. 2011) and reporting to the HFEA is mandatory(HFEA act 2008). Whilst this study is the first to investigate cancer risk after donor ART, it is based on previously published methodology (Williams et al. 2013). There were very few cases with uncertain linkage (n=2), and sensitivity analysis including these did not substantially alter results.

Although this is a population-based study covering the whole of Great Britain over a 17 year time period which includes a large number of children born after donor ART, the rarity of specific diagnostic sub-groups of childhood cancer and thus the small number of cases reported in this study result in wide confidence intervals for individual outcomes. As this is an observational study, it is not possible to adjust for all potential confounders. We have instead used stratification to explore the role of a number of potential moderating and mediating factors, where data are available.

Additionally, this study was not able to compensate for deaths and emigrations within this cohort. However, given the age of the cohort and extrapolating from national data(Office for National Statistics 2010), we would estimate under normal circumstances not more than 69 members of the original cohort would have died during follow-up (0.6%). Emigration rates are harder to estimate, but we assume not more than 2% are likely to have emigrated during follow-up. It was not possible to adjust for socio-economic status (SES) as no measure of SES was available for the cohort as a whole. It is also possible of course that there were other unknown potential confounding factors.

Our study had an average follow-up of 7.86 years. We are not able to comment definitively on risk of cancer subtypes with peak age of onset beyond 7 years.

A significantly increased risk of hepatoblastoma was detected in this study of children born after donor ART, and was associated with low birthweight. A similar increased risk of hepatoblastoma, associated with low birthweight, was seen in our previous study of children born after non-donor conception (SIR 3.64; 95% CI 1.34-7.93) (Williams et al. 2013). The Nordic group found a 2- fold increase risk of hepatic tumours in children born after non-donor ART, but this was based on small numbers and confidence intervals were wide and included 1, they did find a hazard ratio of 2.61 (aHR2.61 (0.74-9.26; adjusted for country, maternal age, parity, sex, gestational age and birth defects) (Sundh et al. 2014). Beckwith-Wiedemann syndrome (BWS) is also a risk factor for hepatoblastoma (Puumala et al., 2012), and children born after ART are at increased risk of BWS(Amor and Halliday 2008). There was a small number of children (<5) in our cohort with BWS, but there were no cases of hepatoblastoma in children with BWS or related anomalies.

There is a known, consistent, inverse association between birth weight and hepatoblastoma risk (O'Neill et al. 2015; Heck et al. 2013; de Fine Licht et al. 2012; Ansell et al. 2005; Spector et al. 2009; Spector et al. 2008; Ikeda, Matsuyama, and Tanimura 1997; McLaughlin et al. 2006; Tanimura et al. 1998). Children born after ART are known to have significantly lower birth weight than children born after spontaneous conception (McDonald et al. 2010; Helmerhorst et al. 2004). Unfortunately as we were unable to adjust for birth weight, instead stratifying for this factor in both studies, we are unable to determine if children in these studies have increased risk of hepatoblastoma mediated solely by their low birth weight or if children born after ART with low birth weight are at higher risk than they would be if born after spontaneous conception at low birth weight. The Nordic study did not adjust for birth weight directly, but adjusted for gestational age, which did not materially alter their rate estimate for hepatic tumours (Sundh et al. 2014).

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222 In conclusion, this study provides evidence against an increased risk of overall childhood cancer in
223 individuals born after donor ART, which is reassuring for parents and clinicians alike. For the majority
224 of individual diagnostic subgroups, risk estimates were not significantly raised. A significant
225 increased risk of hepatoblastoma was observed, in line with that found in our recent study of
226 children born after non-donor ART. This was associated with low birth weight, itself a known risk
227 factor for hepatoblastoma.

228 Despite this finding not being observed in non-UK studies (Sundh et al. 2014; Kallen et al. 2010),
229 further investigation is warranted. It should be emphasised that absolute risks are very small.

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231 **AUTHOR'S ROLES**

232 Dr Williams jointly conceptualized and designed the study, devised the linkage protocol, supervised
233 the linkage and carried out the analysis, drafted the initial manuscript and approved the final
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