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Cancer risk in children born after donor assisted reproductive technology

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

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4 **RUNNING TITLE:** Childhood Cancer after donor ART

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22 **ABSTRACT**

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

25 **Summary answer:** This study showed no overall increased risk of childhood cancer in individuals
26 born after donor ART.

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

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

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

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

47 10.28; 95%CI 1.25-37.14; $P<0.05$). This increased hepatoblastoma risk was associated with low
48 birthweight.

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

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

59 **Study funding/competing interest(s):** This work was funded by Cancer Research UK
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63 Research Group (CCRG) was supported by the charity CHILDREN with CANCER UK, the National
64 Cancer Intelligence Network, the Scottish Government and the Department of Health for England
65 and Wales. There are no competing interests.

66 **Trial registration number:** N/A

67

68 **Key Words:** childhood cancer, assisted reproductive technology, donor treatment, cohort study,
69 epidemiology, data linkage.

70

71

72 INTRODUCTION

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

80 The possibility of an increased risk of childhood cancer in individuals born after ART has been
81 suggested previously (Hargreave et al. 2013; Puumala et al. 2012; Schieve et al. 2004; Sutcliffe and
82 Ludwig 2007; Kallen et al. 2010). Systematic reviews have provided conflicting evidence (Raimondi,
83 Pedotti, and Taioli 2005; Hargreave et al. 2013; Reigstad et al. 2017), with a recent meta-analysis
84 suggesting a small but significant increased risk of cancer in children born after ART (Relative Risk
85 1.33; 95%CI 1.08-1.63) (Hargreave et al. 2013). Two large, population based studies, published since,
86 reported no overall increased risk and no increased risk in haematological cancers (Sundh et al. 2014;
87 Williams et al. 2013). However, these studies did not include children born after donor ART (Sundh
88 et al. 2014; Williams et al. 2013). A further, smaller, population based study showed no overall
89 increased risk of childhood cancer, but did find a significant increase in leukaemia and Hodgkin
90 lymphoma (Reigstad et al. 2016). This study did include some children born after donor ART but did
91 not estimate risk in this group separately (Reigstad et al. 2016).

92 We conducted a large population-based linkage study, aiming to provide risk estimates for childhood
93 cancer overall and for specific diagnostic subgroups (chosen a priori), in individuals born after donor
94 ART.

95

96 MATERIALS AND METHODS

97 Population and cohort participants

98 All records relating to 12,186 children born between January 1st 1992 and December 31st 2008 in
99 Great Britain (England, Wales and Scotland) after donor ART were identified by the Human
100 Fertilization and Embryology Authority (HFEA). Donor ART is defined as 'all treatments or procedures
101 including in-vitro handling of both human oocytes and sperm, or embryos, for the purpose of
102 establishing a pregnancy' using donor oocytes, sperm or embryos (Zegers-Hochschild et al. 2009).
103 The HFEA is legally required to record treatment and outcome details of all ART cycles in the UK,
104 including those using donor gametes or embryos. Thus the dataset is considered effectively
105 complete (HFEA act 2008).

106

107 **Ethical approval**

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

114

115 **Outcome data**

116 Details of cancer incidence were obtained from the National Registry of Childhood Tumours (NRCT).
117 During the study period, the NRCT was the largest national population-based childhood cancer
118 registry world-wide, ascertaining validated information from multiple sources about children, under
119 15 years, diagnosed with cancer in the UK (Kroll et al. 2011). The NRCT is considered almost
120 complete for the study period(Kroll et al. 2011). The International Classification of Childhood Cancer
121 3rd edition (ICCC3), was used to categorise cancers (Steliarova-Foucher et al. 2005). Co-morbidities,
122 known at the time of a child's cancer diagnosis, were reported to the NRCT by the registering
123 oncology centre, and data are reasonably complete for major congenital anomalies.

124

125 **Data linkage**

126 Ethical regulations stipulated that identifiable data were only viewed directly by HFEA staff.

127 Therefore data linkage was undertaken by two members of HFEA staff independently from each

128 other, following a robust data linkage protocol, developed to maximize linkage sensitivity and

129 specificity, used and described in another similar study (Williams et al. 2013). Linkage was directly

130 overseen by CLW, KJB and BB. A total of 12,186 eligible HFEA records of children born after donor

131 ART 1992-2008 were linked to all 14,896 NRCT eligible records of children documented as having

132 been born 1992-2008, and having developed cancer before January 1st 2009. All potential matches

133 using this inclusive linkage protocol were anonymously reviewed by CLW and KJB. BB reviewed any

134 cases where the validity of the match was questionable (n=2, both unanimously rejected by all three

135 reviewers).

136

137 **Statistical analyses and calculation of expected rates**

138 Person-years at risk were calculated from date of birth until the soonest of cancer diagnosis date,

139 December 31, 2008 or the child's 15th birthday. There were 49 children (0.4%) excluded from the

140 analyses as no valid date of birth was available and therefore person-years at risk could not be

141 determined. Expected cancers in the cohort were calculated by multiplying person-years at risk by

142 the corresponding national incidence rates (1-year age bands by calendar year and sex) for children

143 born and diagnosed in Great Britain. Standardized Incidence Ratios (SIR) were calculated comparing

144 observed cancers within the cohort to expected values. Exact 95% confidence intervals and two-

145 sided P values were calculated assuming a Poisson distribution (Breslow and Day 1987). Analyses

146 were performed using STATA software, version 12 (Stata Corp 2013).

147

148

149 **RESULTS**

150 Included in this study were 12,137 children who contributed 95,389 person-years follow-up, with an
151 average duration of 7.86 years. Cohort demographics are detailed in Table 1.

152

153 Twelve children were linked to NRCT records and therefore identified as having developed cancer.
154 Baseline demographics appeared broadly similar for cohort members who did and did not develop
155 cancer (data not shown separately given the small numbers). The median age at cancer diagnosis
156 was 2.6 years (inter-quartile range 1.2-5.2). There were no children with more than one cancer
157 diagnosis. There were 14.4 cancers expected within the cohort, resulting in an unadjusted SIR of 0.83
158 (95% CI 0.43-1.45; Table 2). Sensitivity analysis including the two potential cases rejected during
159 data-linkage did not substantially alter the results (SIR 0.97; 95% CI 0.53- 1.63; data not shown). The
160 results did not change appreciably when stratified by sex, age at diagnosis, birthweight, birth
161 multiplicity, maternal parity, type of ART, and fresh versus cryopreserved embryos (Table 2),
162 although the small number of events in some strata have resulted in wider confidence intervals.

163

164 No significant excess risk was seen for any major ICC3 category, with the exception of hepatic
165 tumours (Table 3). A significant excess of hepatic tumours was detected (SIR 9.12; 95%CI 1.11-32.95;
166 Table 3), all of which were hepatoblastomas (SIR 10.28; 95%CI 1.25-37.14; Table 3; Absolute excess
167 risk 18.66 per million person-years at risk, 95%CI 0.24-73.39). This excess was associated with low
168 birthweight and was only seen in children with birthweight <2500g (SIR 28.00; 95%CI 3.39-101.14; $P=$
169 0.02; data not shown).

170

171 **DISCUSSION**

172 No overall increased risk of childhood cancer was detected in this large and complete national
173 population based cohort of children born after donor ART. This is in line with two similar recently
174 published cohort studies of children born after non-donor ART (Sundh et al. 2014; Williams et al.
175 2013). The recently published study combining data on 91,796 children born after non-donor ART in

176 four Nordic countries found no significant increase in overall cancer rates (adjusted Hazard Ratio
177 1.08; 95%CI 0.91-1.27) (Sundh et al. 2014). Similarly our previous study of 106,013 children born
178 after non-donor ART over the same study period and from the same population as our current study,
179 did not show an overall increased risk of cancer (SIR 0.98; 95%CI 0.81-1.19) (Williams et al. 2013).

180

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

187

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

194 Additionally, this study was not able to compensate for deaths and emigrations within this cohort.

195 However, given the age of the cohort and extrapolating from national data (Office for National
196 Statistics 2010), we would estimate under normal circumstances not more than 69 members of the
197 original cohort would have died during follow-up (0.6%). Emigration rates are harder to estimate,
198 but we assume not more than 2% are likely to have emigrated during follow-up. It was not possible
199 to adjust for socio-economic status (SES) as no measure of SES was available for the cohort as a
200 whole. It is also possible that there were other unknown potential confounding factors, which we
201 were unable to take into account. Whilst the overall numbers of children born after oocyte donation,

202 sperm donation or embryo donation were available, these data were not available for analysis at an
203 individual level. Our study had an average follow-up of 7.86 years. Therefore we are not able to
204 comment definitively on risk of cancer subtypes with a peak age of onset beyond 7 years.

205

206 A significantly increased risk of hepatoblastoma was detected in this study of children born after
207 donor ART, and was associated with low birthweight. A similar increased risk of hepatoblastoma,
208 associated with low birthweight, was seen in our previous study of children born after non-donor
209 conception (SIR 3.64; 95% CI 1.34-7.93) (Williams et al. 2013). The Nordic group found a 2- fold
210 increase risk of hepatic tumours in children born after non-donor ART; although this was based on
211 small numbers and confidence intervals were wide and included 1, they did find a hazard ratio of
212 2.61 (aHR2.61 (0.74-9.26; adjusted for country, maternal age, parity, sex, gestational age and birth
213 defects) (Sundh et al. 2014). Beckwith-Wiedemann syndrome (BWS) is also a risk factor for
214 hepatoblastoma (Puumala et al., 2012), and children born after ART are at increased risk of BWS
215 (Amor and Halliday 2008). There was a small number of children (less than five) in our cohort with
216 BWS, but there were no cases of hepatoblastoma in children with BWS or related anomalies.

217

218 There is a known, consistent, inverse association between birth weight and hepatoblastoma risk
219 (O'Neill et al. 2015; Heck et al. 2013; de Fine Licht et al. 2012; Ansell et al. 2005; Spector et al. 2009;
220 Spector et al. 2008; Ikeda, Matsuyama, and Tanimura 1997; McLaughlin et al. 2006; Tanimura et al.
221 1998). Children born after ART are known to have significantly lower birth weight than children born
222 after spontaneous conception (McDonald et al. 2010; Helmerhorst et al. 2004). Unfortunately as we
223 were unable to adjust for birth weight, instead stratifying for this factor in both studies, we are
224 unable to determine whether children in these studies have increased risk of hepatoblastoma
225 mediated solely due to their low birth weight or whether children with low birth weight born after
226 ART are at higher risk than they would be if born after spontaneous conception. The Nordic study did

227 not adjust for birth weight directly, but adjusted for gestational age, which did not materially alter
228 their rate estimate for hepatic tumours (Sundh et al. 2014).

229

230 In conclusion, this study provides evidence against an increased risk of overall childhood cancer in
231 individuals born after donor ART, which is reassuring for parents and clinicians alike. For the majority
232 of individual diagnostic subgroups, risk estimates were not significantly raised. A significant
233 increased risk of hepatoblastoma was observed, in line with that found in our recent study of
234 children born after non-donor ART. This was associated with low birth weight, itself a known risk
235 factor for hepatoblastoma. Although this finding was not observed in non-UK studies (Sundh et al.
236 2014; Kallen et al. 2010), further investigation is warranted. However it should be emphasised that
237 the absolute risks are very small.

238

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243

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245 Dr Williams jointly conceptualized and designed the study, devised the linkage protocol, supervised
246 the linkage and carried out the analysis, drafted the initial manuscript and approved the final
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248 Mrs Bunch jointly conceptualized and designed the study, devised the linkage protocol, jointly
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251 Mr Charles Stiller jointly conceptualized and designed the study, interpreted data, reviewed and
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262 reviewed and revised the manuscript, and approved the final manuscript as submitted.

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269 the Department of Health for England and Wales.

270

271 **CONFLICT OF INTEREST**

272 There are no conflicts of interest.

273

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Table I. Cohort Characteristics.

Variable	Frequency (%) ¹
N	12,186
Sex	
Male	6,326 (52)
Female	5,851 (48)
Multiple births	
Singletons	6,697 (55)
Multiple Births	5,489 (45)
Birth weight	
Mean (SD) g	2,807 (812)
Birth weight group (g)	
≤2499	3,980 (33)
2500g-3999	7,379 (61)
≥4000	679 (6)
Gestational age at birth	
Mean (SD)	37.1 (3.3)
Type of donor treatment	
Donated oocytes	5209 (43)
Donated sperm	6508 (53)
Donated embryos	469 (4)
Type of ART	
IVF	9,764 (80)
ICSI and other micromanipulation ²	2,110 (17)
Not recorded	310 (3)
Fresh/ frozen cycles	
Fresh Cycle	10,207 (84)
Cryopreserved Cycle	1,949 (16)
Stage at embryo transfer	
Blastocyst	5,402 (44)
Cleavage	370 (3)
Not recorded	6,414 (53)
Maternal age at birth of child	
Mean (SD) years	37.8 (6.2)
Paternal age at birth of child	
Mean (SD) Years	40.3 (7.4)
Infertility cause	
Both Male & Female	2,734 (22)
Female Factor only	2,847 (23)
Male Factor only	4,706 (39)
Unexplained	740 (6)
Not recorded	1,159 (10)
Duration of infertility	
Mean (SD) years	6.1 (4.1)
Previous maternal ART cycles	
0	4,799 (39)
≥1	7,385 (61)
Previous maternal live births	
0	2,546 (21)
≥1	2,535 (21)
Unknown	7,105 (58)

¹Frequencies do not always add up to 12,186, and percentages to 100, where data is unrecorded and treated as missing

²Intracytoplasmic sperm injection (ICSI): a procedure in which a single spermatozoon is injected into the oocyte cytoplasm;

Micromanipulation: a technology that allows micro-operative procedures to be performed on the spermatozoon, oocyte, zygote, or embryo.

Table II. Overall cancer risk stratified by potential mediating/moderating factors.

Mediating/ Moderating Factor	All Cancers ¹		
	Person years follow-up	SIR	95% CI
Overall	95,389	0.83	0.43-1.45
Sex			
Male	49,418	1.13	0.52-2.14
Female	45,970	0.47	0.10-1.36
Age group at diagnosis (years)			
0	11,734	1.29	0.27-3.78
1-4	38,917	0.82	0.30-1.79
5-9	31,688	0.82	0.18-2.57
10-14	13,051	0.00	0.00-2.14
Birth weight (g)			
<2500	33,048	0.80	0.22-2.05
2500g-3999	56,398	0.93	0.40-1.84
≥4000	4,776	0.00	0.00-4.00
Multiple Births			
Singletons	50,331	0.91	0.37-1.87
Multiple Births	45,058	0.74	0.24-1.73
Previous maternal live births			
0	18,940	1.04	0.21-3.03
1 or more	21,165	0.62	0.08-2.25
Type of ART			
IVF	83,548	0.89	0.44-1.58
ICSI and other micromanipulation	10,083	0.00	0.00-1.76
Not recorded	1,734	3.26	0.08-18.2
Fresh/ Cryopreserved cycle			
Fresh	80,153	0.83	0.40-1.52
Cryopreserved	14,830	0.88	0.11-3.18
Not recorded	406	0.00	0.00-55.7

¹Numbers of cancers observed not given, as ethical regulations preclude publishing cells containing fewer than five cohort members.

Table III. Cohort cancer risk by specific cancer type.

Cancer Type and ICCC3 categories ²	Person years of follow up	Standardized Incidence Ratio ¹	95% Confidence Interval
All cancers			
<i>ICCC-3 groups I to X11</i>	95,389	0.83	0.43-1.45
Leukaemia			
<i>ICCC-3 group I</i>	95,445	0.61	0.13-1.78
CNS tumours			
<i>ICCC-3 group III</i>	95,435	1.17	0.32-2.99
Neuroblastoma			
<i>ICCC-3 group IV</i>	95,464	0	0.00-2.03
Retinoblastoma			
<i>ICCC-3 group V</i>	95,452	3.29	0.40-11.87
Renal tumours			
<i>ICCC-3 group VI</i>	95,460	0.94	0.02-5.25
Hepatic tumours			
<i>All- ICCC-3 group VII</i>	95,454	9.12	1.11-32.95*
Hepatoblastoma, ICCC-3 group VIIa	95,454	10.28	1.25-37.14*
Bone tumours and extra osseous sarcomas			
<i>All- ICCC-3 groups VIII and IX</i>	95,464	0	0.00-2.50
<i>Osteosarcoma- ICCC-3 group VIIIa</i>	95,464	0	0.00-18.38
<i>Ewing's Sarcoma- ICCC-3 group-VIIIc, IXd, division 1 & 2</i>	95,464	0	0.00-12.41
<i>Rhabdomyosarcoma- ICCC-3 group IXa</i>	95,464	0	0.00-5.91
<i>Other Sarcomas- ICCC-3 groups VIIIb, VIIIId, VIIIe IXb, IXc, IXd divisions 3 to 11, IXe</i>	95,464	0	0.00-10.45
Germ cell tumours			
<i>ICCC-3 group X</i>	95,464	0.00	0.00-6.59

¹Numbers of cancer observed not given, as ethical regulations preclude publishing cells containing fewer than five cohort members.

²Cancer type classified according to ICCC3 coding²⁹

* = P<0.05. ** =P<0.01*** =P<0.001