Cancer in children and young adults born after assisted reproductive technology: a Nordic cohort study from the Committee of Nordic ART and Safety (CoNARTaS)

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STUDY QUESTION: Do children and young adults born after assisted reproductive technology (ART) have an increased risk of cancer?

SUMMARY ANSWER: Children born after ART showed no overall increase in the rate of cancer when compared with children born as a result of spontaneous conception.

WHAT IS KNOWN ALREADY: Children born after ART have more adverse perinatal outcomes, i.e. preterm births, low birthweights and birth defects. Previous studies have shown divergent results regarding the risk of cancer among children born after ART.

STUDY DESIGN, SIZE, DURATION: A retrospective Nordic population-based cohort study was performed, comprising all children born after ART in Sweden, Denmark, Finland and Norway between 1982 and 2007. The mean (+ standard deviation) follow-up time was 9.5 (4.8) years.

PARTICIPANTS/MATERIALS, SETTING, METHODS: Children born after ART (n = 91 796) were compared with a control group of children born after spontaneous conception. This control group was almost 4-fold the size of the ART group (n = 358 419) and matched for parity, year of birth and country. Data on perinatal outcomes and cancer were obtained from the National Medical Birth Registries, the Cancer Registries, the Patient Registries and the Cause of Death Registries. The cancer diagnoses were divided into 12 main groups. Hazard ratios (HRs) and adjusted HR were calculated. Adjustments were carried out for country, maternal age, parity, sex, gestational age and birth defects.

MAIN RESULTS AND THE ROLE OF CHANCE: There was no significant increase in overall cancer rates among children born after ART when compared with children born after spontaneous conception (adjusted HR 1.08; 95% CI 0.91 – 1.27). Cancer, of any form, was found among 181 children born after ART (2.0/1000 children, 21.0/100 000 person-years) compared with 638 children born after spontaneous conception (1.8/1000 children, 18.8/100 000 person-years). Leukaemia was the most common type of cancer (n = 278, 0.62/1000 children) but no significantly increased incidence was found among children born after ART. An increased risk was observed for 2 of 12 cancer groups.
Cancer rates in children born after ART

Introduction

It is well known that children born after assisted reproductive technology (ART) have more adverse perinatal outcomes, e.g. preterm births, low birthweights and birth defects, when compared with spontaneously conceived (SC) children (Helmerhorst et al., 2004; Jackson et al., 2004; Hallday, 2007; Pinborg et al., 2013). However, there are few well-designed studies on long-term outcomes of children born after ART (Hart and Norman, 2013a,b).

Divergent results on cancer risk in children born after ART have been reported in the literature. A systematic review and meta-analysis from 2005 including 11 studies showed no overall increased risk of cancer among children born after ART (standardized incidence ratio (SIR) 1.33; 95% CI 0.62–2.85) (Raimondi et al., 2005). However, a recent systematic review and meta-analysis (Hargreave et al., 2013) indicated a significantly increased risk of all cancers in children born after all kinds of fertility treatment ([relative risk] 1.33; 95% CI 1.08–1.63)]. Also, in a subset of children born after ART, the risk of cancer was increased (RR 1.40; 95% CI 1.12–1.74). Significant associations were found for haematological cancers, central nervous system (CNS)/neural tumours and other solid cancers, and for specific cancer types such as leukaemia, neuroblastoma and retinoblastoma. Among earlier cohort studies, Källén et al. (2010a) in a large study from Sweden (n = 26 692 children born after ART) reported a significantly increased risk of cancer among children born after ART, compared with children conceived after spontaneous conception (odds ratio (OR) 1.42; 95% CI 1.09–1.87). Recently, in a large cohort study comprising 106 013 children born in Britain after ART, no increase in the overall risk of cancer was found (SIR 0.98; 95% CI 0.81–1.19). In subgroup analyses, however, increased risks of hepatoblastoma and rhabdomyosarcoma were detected, although the absolute risks were small (Williams et al., 2013). Hence, it is unclear whether children born after ART have an increased risk of developing cancer in childhood.

The aim of this study was to determine the risk of cancer in a large cohort of children and young adults conceived by ART in the Nordic countries between 1982 and 2007. The study was the result of a collaborative effort by members of CoNARTaS (Committee on Nordic ART and Safety) part of which has been presented previously (Henningsson et al., 2011).

Materials and Methods

Data sources

We used a Nordic, population-based cohort of all children born after ART in Sweden, Denmark, Finland and Norway (n = 91 796). Data were collected from the national ART registers and Medical Birth Registers (MBRs), both with close to 100% coverage (Henningsson et al., 2011). Data were included from the year registration of ART children commenced in each country, until December 2007. Children born as a result of ART included singletons and multiples born after in vitro fertilization (IVF), intracytoplasmic sperm injection (ICSI) and frozen embryo transfer (FET). The unique personal identification number assigned at birth allowed each individual registered in the national ART registers to be linked to the national MBRs. Using the MBRs, children born after ART (singletons and multiples) were matched 1:4 with a control group from the MBR of SC children from their own country. The matching criteria were parity (parity 0 versus parity ≥1) and year of birth. Children conceived after fertility treatments other than ART are included among the controls, since it was not possible to identify them.

Through personal identification numbers, links were established to other population-based registers in each country: the Cancer Registers, the Patient Registers and the Cause of Death Registers. Data on cancer diagnoses were collected from the Cancer Register and the Patient Register in Sweden, from the Patient Registers in Denmark and Finland and from the Cancer Register in Norway. Data on cancer diagnoses were collected until 1 September 2010 in Sweden, until 31 December 2011 in Denmark, until 31 December 2007 in Finland and until 31 December 2012 in Norway. The main reason for the differences in time period for data collection between the countries was varying difficulties in getting permissions for data extraction and data export.

The Nordic health data registers are extensively used for research purposes and several validations have been performed and the quality has been deemed to be satisfactory (Andersen et al., 1999; The Swedish Board of Health and Welfare, 2003; Barlow et al., 2009; Larsen et al., 2009; Ludvigsson et al., 2011; Lynge et al., 2011; Sund 2012).

Classification of cancer diagnosis

From the registers, we identified children with a cancer diagnosis according to the International Classification of Diseases (ICDs). ICD 9 comprises 140–209 codes and ICD 10 comprises C00–C96 codes. Cancer diagnoses were grouped into 12 main groups according to the International Classification of Childhood Cancer (ICCC-3) and ICD codes: I. leukaemias (C91–C96), II. lymphomas (C81–C85), III. CNS tumours (C70–C72, C751,
C759, C76, C80) (Steliarova-Foucher et al., 2005). All cancer diagnoses were grouped by a specialist in paediatric oncology (B.L.).

Definitions
Preterm birth was defined as a gestational age < 37 weeks, very preterm birth as < 32 weeks, postterm birth as ≥ 42 weeks, low birthweight as < 2500 g, very low birthweight as < 1500 g and macrosomia as ≥ 4500 g. Small for gestational age (SGA) was defined as more than two standard deviations (SDs) below the Swedish gestational age- and sex-specific growth standard and large for gestational age (LGA) as more than two SDs above the Swedish growth standard (Marsal et al., 1996).

Children with birth defects and chromosomal aberrations were defined as children with a relevant ICD 9 (740–759) or ICD 10 (Q00–99) code.

No child born after ART had more than one cancer diagnosis. Four children in the control group had two recorded diagnoses of cancer.

In the ART group, children with cancer were more often twins (P = 0.046), had a lower gestational age (P = 0.04), more birth defects (P = 0.04) and more chromosomal aberrations (P < 0.0001) than children without cancer.

In the spontaneous conception group, children with cancer had a higher rate of preterm birth (P = 0.01) low birthweight (P = 0.006), very low birthweight (P = 0.04), LGA (P = 0.003), birth defects (P < 0.0001) and chromosomal aberrations (P < 0.0001) (Table I).

Cancers with cancer (total group, ART and spontaneous conception) had higher rates of preterm birth (P = 0.001), low birthweight (P < 0.0001), LGA (P = 0.003), birth defects (P < 0.0001) and chromosomal aberrations (P < 0.0001) than children without cancer.

The mean (± SD) length of follow-up was 9.5 (4.7) years for all children. It was 9.6 (4.8), 9.5 (3.4), 7.3 (4.3) and 11.9 (5.0) years for children born in Sweden, Denmark, Finland and Norway, respectively.

Cancer in general
With our data, we did not show that ART increases the risk of childhood cancer (adjusted HR 1.08; 95% CI 0.91–1.27). Among children born between 1982 and 2007, we found 181 children born after ART (2.0/1000 children) and 638 children born after spontaneous conception (1.8/1000 children) with any form of cancer diagnosis. The cancer incidence per 100 000 person-years of observation was 21.0 in children born after ART and 18.8 in children born after spontaneous conception.

The cancer incidence in the different countries is shown in Table II. The cancer incidence in children born after ART was 2.0, 2.4, 1.1 and 2.3/1000 children in Sweden, Denmark, Finland and Norway, respectively.

The corresponding figures among children born after spontaneous conception were 1.6, 2.1, 1.7 and 1.8/1000 children, respectively. The mean (± SD) age at diagnosis was 5.6 (4.7) years for children born after ART and 4.9 (4.1) years for children born after spontaneous conception.

The mortality rate in children with cancer was 14.4% (26/181) in children born after ART, and 10.2% (65/638) in children born after spontaneous conception (1.8/1000 children). The mean (± SD) age at death in children with cancer was 5.1 (3.9) years in children born after ART and 5.3 (4.3) years in children born after spontaneous conception.

Types of cancer
The types of cancer are presented in Tables III and IV.

The most common type of cancer was leukaemia, which occurred in 278 of all children (0.62/1000 children). No significantly increased risk of leukaemia was found in children born after ART when compared with children born after spontaneous conception.

The second most common type of cancer was CNS tumours, which occurred in 156 children (0.35/1000 children) (Table III). A significantly higher risk of CNS tumours was found in children born after ART when compared with children born after spontaneous conception (adjusted HR 1.44; 95% CI 1.01–2.05) (Table IV). The absolute risk of a CNS tumour among children born after ART was 0.46/1000 children and 0.32/1000 children for those born after spontaneous conception.

We also found a higher risk of malignant epithelial neoplasms for children born after ART compared with children born after spontaneous conception (adjusted HR 2.03; 95% CI 1.06–3.89). Malignant epithelial neoplasms occurred in 0.15/1000 of children born after ART and in 0.07/1000 children born after spontaneous conception (Table IV).

Results
Characteristics of the cohort
Baseline demographic characteristics are presented in Table I for children born after ART, with and without cancer, and for children born after spontaneous conception, with and without cancer.
Malignant melanomas or other malignant skin tumours were the most common diagnoses in this group (10/14 in ART group and 20/26 in spontaneous conception group).

**Discussion**

The main finding in this large study based on national registers, which included almost 92 000 children born after ART in four Nordic countries between 1982 and 2007, was that no overall higher incidence of cancer was found among children born after ART when compared with children born after spontaneous conception. We detected 181 cancer cases in children born after ART (2.0/1000 children) and 638 cases born after spontaneous conception (1.8/1000 children) corresponding to an adjusted HR of 1.08 (95% CI 0.91–1.27). For 2 of the 12 studied cancer types, CNS tumours and malignant epithelial neoplasms, we observed a significantly increased risk among ART children. Generally, significant differences in subanalyses should be interpreted with caution when no significant differences have been found in the main analysis. However, different cancers may have different aetiologies and thus it may be conceivable that the cancer risk for children born after ART could be increased for some cancers while no overall increased risk is observed. While some studies have reported an increased risk of some types of cancer in children born after ART, e.g. leukaemia, rhabdomyosarcoma and hepatoblastoma, no general pattern has been observed (Petridou et al., 2012, Williams et al., 2013). In the systematic review of Hargrave et al. (2013), excluding neural tumours and restricting the analysis to CNS tumours, no significant increase was found in children born after ART. Neither in the large UK study, was any increase in CNS tumours found (Williams et al., 2013).

Safety aspects for children born after ART are of major importance, particularly due to the widespread use of the IVF techniques, resulting in more than 5 million children worldwide (Adamson et al., 2013). While a poorer obstetric outcome, assessed as low birthweight and a higher rate of preterm birth (Helmerhorst et al., 2004; Jackson et al., 2004;...
Table II Children with cancer by mode of conception and country of living

<table>
<thead>
<tr>
<th>Country</th>
<th>ART</th>
<th>Total per 100,000 boys</th>
<th>Person-years</th>
<th>With cancer</th>
<th>Total per 100,000 children</th>
<th>Person-years</th>
<th>With cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sweden</td>
<td>32 691</td>
<td>1 563 094</td>
<td>17.6</td>
<td>66 2.0</td>
<td>311 562</td>
<td>21.2</td>
<td>131 043</td>
</tr>
<tr>
<td>Denmark</td>
<td>23 422</td>
<td>1 028 851</td>
<td>23.0</td>
<td>67 997</td>
<td>21.2</td>
<td>84 870</td>
<td>23.6</td>
</tr>
<tr>
<td>Finland</td>
<td>18 944</td>
<td>594 449</td>
<td>15.3</td>
<td>75 972</td>
<td>14.6</td>
<td>79 958</td>
<td>15.5</td>
</tr>
<tr>
<td>Norway</td>
<td>16 739</td>
<td>107 870</td>
<td>24.4</td>
<td>68 972</td>
<td>14.6</td>
<td>84 870</td>
<td>23.6</td>
</tr>
<tr>
<td>Total</td>
<td>91 796</td>
<td>3 401 291</td>
<td>18.8</td>
<td>358 419</td>
<td>18.8</td>
<td>358 419</td>
<td>18.8</td>
</tr>
</tbody>
</table>

McDonald et al., 2009; Pinborg et al., 2013), and also a higher rate of congenital anomalies (Källén et al., 2010b, Davies et al., 2012; Hansen et al., 2013) have consistently been shown for children born after ART, more divergent results have been presented concerning childhood cancer. In a recent systematic review from Denmark (Hargreave et al., 2013), including 25 studies of varying quality, a significantly higher risk of cancer and several cancer subtypes, was found among children born after ART. However, confined to cohort studies, the results have been less clear. Only one cohort study, a study from Sweden including 26 692 ART children born between 1982 and 2005, and included in this review, found an increased risk of cancer among ART children (Källén et al., 2010b) (OR 1.42; 95% CI 1.09 – 1.87). In all, 53 cases of cancer were identified among children born after ART, against 38 expected cancers. There were six cases of histiocytosis against 1.0 expected. Excluding the histiocytosis cases reduced the OR to 1.34, but it remained significant. None of the other cohort studies included in this systematic review (White et al., 1990; Rufat et al., 1994; Doyle et al., 1998; Bruinsm et al., 2000; Lerner-Geva et al., 2000; Klip et al., 2001; Odone-Filho et al., 2002;Brinton et al., 2004; Pinborg et al., 2004), including between 176 and 9479 children born after ART, found an increase in total cancer risk for the children born after ART compared with children born after spontaneous conception.

More recently, a large cohort study from the UK was published (Williams et al., 2013). This study consisted of more than 106 000 ART children, born between 1992 and 2008 with an average follow-up of 6.6 years. Overall, 108 cases of cancer were found compared with 109.7 expected cancers (SIR 0.98; 95% CI 0.81 – 1.19). Although they found a significantly increased incidence of two subtypes of cancer (rhabdomyosarcoma and hepatoblastoma), their overall conclusion was ‘no overall higher risk of cancer among children born after ART’.

In the present study, the cancer incidence differed somewhat between the different Nordic countries. This difference might, at least partly, depend on the different lengths of follow-up periods. It should also be noted that the incidence of cancer was higher in this study than in the UK study (Williams et al., 2013). Here too, this difference is probably due to the difference in length of follow-up periods, being 6.6 years in the UK study compared with 9.5 years in the present study. Other reasons for differences in cancer incidence may be the ways of collecting data. In the present study, full identification of all individuals was available, making linkage with population registers possible. The Nordic Registries are known to have high validity, achieving almost 100% population coverage.

Among children with a cancer diagnosis, significantly higher rates of low gestational age, birth defects and chromosomal aberrations were observed, both among ART children and children born after spontaneous conception, when compared with children without a cancer diagnosis. This is well known from other studies (Hasle, 2001; Feusner and Plaschkes, 2002, McLaughlin et al., 2006; Podvin et al., 2006; Spector et al., 2009; Källén et al., 2010a; Rudant et al., 2013) and in the multivariate analysis, we adjusted for these variables as confounders.

The main strength of this study is its large sample size, complete ascertainment of cancer diagnosis, the use of high-quality population registries and the inclusion of a control group based on SC children, drawn from the total population of births within each of the four participating countries. The inclusion of four different Nordic countries may be regarded as both a strength, since it increases the generalizability, but also a limitation due to the heterogeneity of data. A further limitation is the fact that it was not
possible to adjust for other potential confounders such as socio-economical status, maternal smoking, maternal pre-pregnancy body mass index and perinatal health status, e.g., Apgar score. These are all variables which have been suggested to affect cancer rates in other studies (Buck et al., 2001; Spector et al., 2005; McLaughlin et al., 2006; Adam et al., 2008; Källén et al., 2010a; Schmidt et al., 2010); however, it is unlikely that they would act as strong confounders in our setting.

In conclusion, this large Nordic study of cancer among children born after assisted reproduction, using national registers as data sources, shows no overall higher risk among children born after ART compared to spontaneous conceptions.
with children born after spontaneous conception. This information is reassuring for couples undergoing ART, the children born after ART and clinicians working with ART. The study, however, also stresses the need for continuous follow-up of children born after ART, particularly for uncommon conditions and after newly introduced techniques.

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Authors’ roles
All authors contributed to the conception and design of the study. U.-B.W., A.A.H., A.P., L.B.R., R.S. and M.G. collected the data from the National Registries. All cancer diagnoses were grouped by B.L., K.K. performed the statistical analyses. U.-B.W., C.B. and K.J.S. contributed to the analysis and interpretation of data. U.-B.W., C.B. and K.J.S. drafted the manuscript and revised it. All the authors approved the final version.

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Conflict of interest
None declared.

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