Adverse obstetric outcomes among female childhood and adolescent cancer survivors in Sweden: A population-based matched cohort study

Gabriela Armuand, Agneta Skoog Svanberg, Marie Bladh and Gunilla Sydsjö

Armuand, G., Skoog Svanberg, A., Bladh, M., Sydsjö, G., (2019), Adverse obstetric outcomes among female childhood and adolescent cancer survivors in Sweden: A population-based matched cohort study, *Acta Obstetricia et Gynecologica Scandinavica*. https://doi.org/10.1111/aogs.13690

Original publication available at:
https://doi.org/10.1111/aogs.13690

TITLE PAGE

Adverse obstetric outcomes among female childhood and adolescent cancer survivors in Sweden: a population-based matched cohort study

Gabriela Armuand[1] PhD, Agneta Skoog Svanberg[2] PhD, Marie Bladh[1] PhD and Gunilla Sydsjö[1] PhD

[1] Department of Clinical and Experimental Medicine, Faculty of Health Sciences, Linköping University, Linköping, Sweden

[2] Department of Women's and Children's Health, Uppsala University, Akademiska sjukhuset, Uppsala, Sweden

Corresponding author: Gabriela Armuand, Linköping University, Department of Clinical and Experimental Medicine, Obstetrics and Gynecology, SE-581 85 Linköping, Sweden; +46 (0)733-727401, gabriela.armuand@gmail.com

CONFLICT OF INTEREST

There are no conflicts of interest in connection with this article.

FUNDING

The study has not received any research funding.

KEYWORDS

Cancer survivors; Cesarean Section; Delivery, Obstetric; Pre-eclampsia; Pregnancy, high-Risk; Labor, induced; Childhood; Adolescence

ABBREVIATIONS

ANOVA, Analysis Of Variance; aOR, adjusted Odds Ratio; ART, Assisted Reproductive Technology; CI, Confidence Interval; CVS, Chorionic Villus Sampling; CS, Cesarean section; ICD, International Classification of Diseases; IOL, Induction of Labor; IVF, In Vitro Fertilization; MBR, the Swedish Medical Birth Register; NPR, the National Patient Register; OR, Odds Ratio: SD, Standard Deviation; TPR, the Total Population Register; VE, Vacuum Extraction

KEY MESSAGE

The higher risk of adverse obstetric outcomes among pediatric cancer survivors calls for strict monitoring during pregnancy and childbirth.

ABSTRACT

Introduction: Cancer treatment during childhood may lead to late adverse effects, such as reduced musculoskeletal development, or vascular, endocrine and pulmonary dysfunction, which in turn may have an adverse effect on following pregnancy and childbirth. The aim of the present study was to investigate pregnancy and obstetric outcomes as well as the offspring's health among childhood and adolescent female cancer survivors.

Material and methods: This register-based study included all women born between 1973 and 1977 diagnosed with cancer in childhood or adolescence (age <21), as well as an age matched comparison group. A total of 278 female cancer survivors with first childbirth were included in the study, together with 829 age-matched individuals from the general population. Logistic regression and analysis of variance were used to investigate associations between having been treated for cancer and the outcome variables, adjusting for maternal age, nicotine use and comorbidity.

Results: Survivors were more likely to have pre-eclampsia (adjusted Odds Ratio [aOR] 3.46, 95% confidence interval [CI] 1.58-7.56), undergo induction of labor (aOR 1.66, 95% CI 1.05-2.62), suffer labour dystocia (primary labour dystocia aOR 3.54, 95% CI 1.51-8.34 and secondary labour dystocia aOR 2.43, 95% CI 1.37-4.31), malpresentation of foetus (aOR 2.02, 95% CI 1.12-3.65), and imminent fetal asphyxia (aOR 2.55, 95% CI 1.49-4.39). In addition, deliveries among survivors were more likely to end with vacuum extraction (aOR 2.53, 95% CI 1.44-4.47) with higher risk of clitoral lacerations (aOR 2.18, 95% CI 1.47-3.23) and anal sphincter injury (aOR 2.76, 95% CI 1.14-6.70) and emergency cesarean section (aOR 2.34 95% CI 1.39-3.95). Also, survivors used pain reliving methods to a higher extent compared to the comparison group. There were no increased risk of neonate diagnoses and malformations. The results showed that survivors who had been diagnosed with cancer when they were younger than 14 had increased risks of adverse obstetric outcomes.

Conclusions: The study demonstrates increased risk of pregnancy and childbirth complications among childhood and adolescent cancer survivors and there is a need to optimize the perinatal care, especially among survivors who were younger than 14 at time of diagnosis.

INTRODUCTION

Thanks to the development of effective cancer treatments, the majority of female cancer patients diagnosed during childhood and adolescence will survive. However, many of the treatment regimens are gonadotoxic, and the probability of survivors having children is lower compared with their siblings (1-4) and the general population (5-8). Over all, there is little knowledge about possible pregnancy and childbirth complications. A study from the United Kingdom including 1712 women found an increased risk of hypertension during pregnancy as well as gestational diabetes mellitus among childhood cancer survivors (9). Survivors were also more likely to undergo induction of labor (IOL) (10) as well as cesarean section (CS) (9, 10). As concerns different age groups, women diagnosed with cancer during childhood (age 0–14 years) had a higher risk of developing obstetric complications compared to female siblings (10).

The aim of the present study was to investigate pregnancy and obstetric outcomes as well as the offspring's health among childhood and adolescent female cancer survivors and to compare these outcomes with an age-matched comparison group.

MATERIAL AND METHODS

Data sources

In the present study, five population-based registries were used. *The National Patient Register* (NPR) contains information about main and secondary diagnoses for all in-patients in Sweden. By using NPR all women born between 1973 and 1977 diagnosed with cancer in childhood or adolescence (age <21) were identified (N=576). As the NPR data used in the present study consist of the International Classification of Diseases version 8 and 9 (ICD-8 and ICD-9), the codes were converted into ICD-10 in order to obtain clear definitions. *The Total Population Register* (TPR) was used to create a comparison group consisting of two age matched women per case (born-on-the-same-day). TPR also contains information on marital status and migration. The individuals in the comparison group (N=1152) were assigned a referent date corresponding to the date of cancer diagnosis of the cancer survivor. *The Swedish Medical*

Birth Register (MBR), established in 1973, was used to gain information about involuntary childlessness, prenatal, delivery and neonatal complications and care of the participants' first live birth. The following definitions were used: Involuntary childlessness was defined as failure to achieve pregnancy after 12 months or more; Pregnancy hypertension was defined as blood pressure ≥ 140/90 mmHg after 20 weeks' gestation without proteinuria; Pre-eclampsia was defined as blood pressure ≥ 140/90 mmHg after 20 weeks' gestation with proteinuria; Gestational diabetes was defined as onset or first recognition of impaired glucose tolerance or manifest diabetes during pregnancy; Anemia was defined as hemoglobin < 100 g/L. The following definitions regarding delivery complications were used: Primary labour dystocia was defined as dilatation of the cervix with <1 cm/hr during active phase; Secondary labour dystocia was defined as no progress ≥ 2 hours after initially normal progress; Imminent fetal asphyxia was defined as indications of fetal distress leading to an intervention (e.g. vacuum extraction [VE] or emergency CS); Malpresentation of fetus was defined as all presentations other than vertex; Emergency CS was defined as delivery that started without a CS but ended with one; Postpartum hemorrhage was defined as ≥ 1,000 ml bleeding within 24 hours after childbirth; Placental complication was defined as including placental abruption, placenta previa, placenta accreta and retained placenta/membranes; Lacerations with no distinction between lacerations of skin and/or muscle;. The following definitions regarding neonatal outcomes were used; APGAR-scores were dichotomized into ≤7 and >7; Small for gestational age was defined as birth weight ≤ 2 SD of the mean weight for gestational length; Large for gestational age was defined as birth weight ≥ 2 SD of the mean weight for gestational length. Through MBR we also obtained information about comorbidity, nicotine use during pregnancy and pain relieving methods during childbirth. Having children after cancer/referent date was defined as giving birth to a child at age 13 or older with the last menstruation coinciding with the first cancer diagnosis/referent date or later. The age of 13 was chosen as start of follow-up as the average age of menarche in Sweden is about 13 years of age. Also, the youngest girls noted in the registry as having given birth are 13 years of age. Only data originating from the first childbirth was included. *The Swedish Register of Education* was used to obtain information about the participants' educational level. In addition, *The IVF register* was used to identify women who had undergone in vitro fertilization (IVF) treatment and subsequently given birth (11). The register also includes information on use of donor oocytes. The women were followed from age 13 until date of death, permanent emigration, first childbirth or

December 31, 2012. Subsequently the women included in the study gave birth between 1986 and 2012.

Statistical analysis

Pearson's Chi-square or t-test was used to investigate the relationship between variables. To determine if cancer in childhood or adolescence was related to various aspects of obstetric outcomes (conception, pregnancy, childbirth and the offspring's health) logistic regression or ANOVA (Analysis Of Variance) was used. Adjustments were made for maternal age, nicotine use and comorbidity (Table 1).

In order to investigate the possible effect of age at time of diagnosis on obstetric outcomes in the participants first live birth, data were stratified into two age groups; childhood (<14 years) and adolescence (≥14-20 years). In addition, sub-group analysis were performed to investigate if cancer type had any impact on reproductive outcomes. To reach enough power, single diagnoses were brought together to form three major diagnostic groups; *Hematological malignancies* (n=77, ICD-10 C81-C88, C91-C95), *Malignant neoplasms of nervous and endocrine systems* (n=71, ICD-10 C69-C75) and *Bone and articular cartilage, and genitourinary malignancies* (n=74, ICD-10 C40-C41, C51-C58, C64-C68). Individuals who had received more than one diagnosis (n=30) were included in each subset of the appropriate diagnostic group. Statistical analyses were conducted in SPSS (IBM Corp. Released 2013. IBM SPSS Statistics for Windows, Version 22.0, Armonk, NY). P <.05 was used to indicate statistical significance.

Ethical approval

This study was approved by the Regional Ethical Review Board, Linköping, Sweden. No. 03-556, 03-557, 07-M66 08 – 08-M 233-8, 2010/403-31, 2014/112-31.

RESULTS

Between 1973 and 1977 a total of 516 576 individuals were born in Sweden. Of these, a total of 576 girls were diagnosed with cancer before the age of 21 (0.1%). Among the 552 girls/women who were alive and resident in Sweden past the age of 13, 278 gave birth to at least one live child after diagnosis (50.4%) and were consequently included in the study.

Cancer survivors were younger when they had their first live birth compared with the comparison group (P <0.001) (Table 1). More detailed information about reproductive patterns among the female survivors in the present study is presented elsewhere (7). The majority of the survivors had been diagnosed during childhood (60.8%).

Conception and pregnancy

While the survivors more often had experienced involuntary childlessness before giving birth, there were no differences between the groups regarding use of assisted reproductive technology (ART), use of donor oocytes or a history of spontaneous abortions (Table 1). During pregnancy, survivors were three times more likely to be diagnosed with pre-eclampsia compared to the comparison group (Table 2), even after controlling for maternal age, nicotine use and comorbidity. When comparing survivors with the comparison group, the severity of the pre-eclampsia did not differ significantly: pre-eclampsia with onset during labour, n=1 vs n=1, light to moderate pre-eclampsia, n=12 vs n=10, severe pre-eclampsia, n=3 vs n=4 and HELLP syndrome, n=2 vs n=2).

Sub-group analysis showed that individuals with a history of hematological malignancy were more likely to have been diagnosed with pre-eclampsia during pregnancy compared with the comparison group (10.4% vs 2.2%, P=0.015, adjusted odds ratio [aOR) 4.66, 95% confidence interval [CI] 1.34-16.21), as was also the case among those with a history of malignant neoplasms of nervous and endocrine systems (4.2% vs 0.4%, P=0.040, aOR 13.02, 95% CI; 1.13-150.53) and those who had been diagnosed with cancer when younger than 14 years (5.9% vs 1.3%, P<.001, aOR 6.96, 95% CI; 2.34-20.69). There was no significant difference between survivors and comparisons with diagnostic date/referent date at 14-20 years of age.

Labour and Delivery

When controlling for maternal age, nicotine use, and comorbidity, survivors were between two to almost four times more likely to suffer from primary and secondary labour dystocia, as well as being more likely to have malpresentation of the fetus and imminent fetal asphyxia (Table 2). The deliveries among survivors were more likely to be ended with VE or emergency CS. Survivors were also more likely to suffer from clitoral lacerations and anal sphincter injuries (Table 2). As there is a known risk of laceration in connection with VE an in-depth analysis was performed to investigate the relationship between VE and lacerations (all types of lacerations combined). When controlling for VE in addition to maternal age, nicotine use, and

comorbidity the difference in likelihood of lacerations between survivors and comparison group disappeared (*P*=0.64, aOR 1.62, 95% CI; 0.97-2.69).

During childbirth, the survivors more often used epidural analgesia and local anesthesia, as well as systemic pain-relieving methods such as opioids and sedatives (Table 3). As pre-eclampsia was elevated among cancer survivors an in-depth analysis was performed to investigate its impact on IOL. When controlling for pre-eclampsia in addition to maternal age, nicotine use, and comorbidity, the difference in IOL between cancer survivors and comparison group disappeared (*P*=0.102, aOR 1.48, 95% CI; 0.93-2.36). Also, as IOL increases the risk for emergency CS an in-depth analysis was performed to investigate its impact on CS. When controlling for IOL in addition to maternal age, nicotine use, and comorbidity, the difference in emergency CS between cancer survivors and comparison group remained (*P*=0.006, aOR 2.10, 95% CI; 1.24-3.56).

Sub-group analysis showed that individuals with a history of hematological malignancy were less likely to have a spontaneous start of delivery (74.0% vs 80.2%, *P*=0.035, aOR 0.48, 95% CI; 0.24-0.95) and more likely to be induced (18.2% vs 9.7%, *P*=0.008, aOR 3.01, 95% CI; 1.34-6.77) compared with the comparison group. Their delivery was also more likely to end with VE (13.0% vs 6.2%, *P*=0.013, aOR 3.47, 95% CI; 1.30-9.26), and cancer survivors had an increased risk for clitoral lacerations (24.7% vs 13.2%, *P*=0.002 aOR 3.05, 95% CI; 1.49-6.25) and postpartum hemorrhage (14.3% vs 7.0%, *P*=0.039, aOR 2.55, 95% CI; 1.05-6.21). Individuals treated for bone and articular cartilage, and genitourinary malignancies were more likely to have primary labor dystocia (5.4% vs 1.5%, *P*=0.026, aOR 7.03, CI; 1.27-38.96) compared to the comparison group. They were also more likely to have imminent fetal asphyxia (12.2% vs 6.3%, *P*=0.026, aOR 3.27, CI; 1.15-9.27), and to have their delivery ended with VE (8.1% vs 4.4%, *P*=0.047, aOR 3.57, CI; 1.02-12.54) or emergency CS (17.6% vs 7.3%, *P*=0.005, aOR 3.73, CI; 1.50-9.29). In addition, they more often suffered from clitoral laceration (21.6% vs 14.6%, *P*=0.041, aOR 2.24, 95% CI; 1.03-4.88) and anal sphincter injury (9.4% vs 2.4%, *P*=0.031, aOR 4.76, 95% CI; 1.15-19.61).

Childhood cancer survivors were more likely to undergo IOL (15.4% vs 11.0%, *P*=0.006, aOR 2.19, 95% CI; 1.25-3.85), having primary dystocia (4.7% vs 1.9%, *P*=0.009, aOR 4.11, 95% CI; 1.42-11.88) and secondary labor dystocia (11.2% vs 5.5%, *P*=0.003, aOR 2.85, 95% CI; 1.43-5.71) compared with the comparison group. They were also more likely to have imminent fetal asphyxia (11.8% vs 5.1%, *P*<0.001, aOR 3.30, 95% CI; 1.65-6.60), and to

have their delivery ended with VE (10.7% vs 4.9%, *P*<0.001, aOR 3.53, 95% CI; 1.72-7.24) or emergency CS (10.7% vs 6.0%, *P*=0.003, aOR 2.85, 95% CI; 1.44-5.65). They were also more likely to suffer from clitoral laceration (18.9% vs 14.9%), *P*=0.028, aOR 1.77, OR95% 1.06-2.95). There were no significant difference between survivors and comparisons with diagnostic date/referent date at 14-20 years of age.

Neonatal health

There were no cases of perinatal death in the sample. Survivors were more likely to have a preterm birth, but this did not remain statistically significant after controlling for maternal age, nicotine use and comorbidity (Table 4). The babies of survivors were smaller compared to babies born by the comparison group. There were no differences between the groups regarding neonate diagnoses, APGAR-scores and the proportion of malformation.

However, sub-group analysis showed that babies of survivors of hematological malignancy were more likely to have low APGAR-scores 5 minutes after birth compared to those born by the comparison group (n=4, 5.2% vs n=1, 0.4%, *P*=0.018, aOR 16.39, 95% CI; 1.61-166.67). Also, childhood cancer survivors were more likely to have a baby that was small for gestational age (n=16, 4.0% vs n=15, 2.2%, *P*=0.002, aOR 6.42, 95% CI; 2.00-20.59). There was no significant difference between survivors and comparisons with diagnostic date/referent date at 14-20 years of age.

DISCUSSION

The present study found that cancer survivors had higher rates of pre-eclampsia, IOL, labor dystocia, imminent fetal asphyxia, VE and emergency CS in connection with their first live birth compared to the age-matched comparison group. The results also indicates that childhood cancer survivors (diagnosed when younger than 14) were an especially vulnerable group.

There are some studies investigating pre-eclampsia among cancer survivors, but the results are conflicting. A US study among 1894 female survivors of adolescent and young adult cancer showed an increased risk of preeclampsia (aOR 1.32, 95% CI 1.04–1.87) (12), and another US study of 1898 female childhood and adolescent cancer survivors reported a borderline estimate of increased pre-eclampsia (aOR 2.57, 95% CI 0.99-6.68) (13). Conversely, a Scottish among

917 women with a previous history of cancer showed no elevated levels of preeclampsia (aOR 1.07 95% CI 0.78–1.48) (14). This was also the case in a Finnish study among 1753 female cancer survivors (diagnosed below 40 years of age) where the overall risk for pre-eclampsia was not increased (aOR 1.11, 95% CI 0.85–1.45) (15). There are several risk factors for developing pre-eclampsia where being overweight or obese are the most important factor (16). It is known that childhood cancer survivors more often suffer from obesity (17). Regrettably, due to a high degree of missing values, we could not adjust for maternal weight. Pre-eclampsia during pregnancy is a potentially severe complication that may lead to maternal and fetal morbidity, and it therefore constitutes one of the indication for IOL (18). In the present study, the survivors were at higher risk of undergoing IOL and a post-hoc analysis showed that pre-eclampsia was associated with the elevated levels of IOL. Research on women with no cancer history has shown that IOL is associated with adverse maternal and neonatal outcomes, such as instrumental delivery, CS and low APGAR-score at 5-min (19) - outcomes elevated among survivors in our study. Knowing that cancer survivors may have an increased risk of pre-eclampsia could therefore lay the ground for individualized screening routines with the aim of early detection of elevated blood pressure and proteinuria, and initiation of interventions to reduce morbidity.

Survivors were between two to almost four times more likely to suffer from labor dystocia, imminent fetal asphyxia and malpresentation. This is in conflict to previous findings where there were no increased risks of labor dystocia, fetal stress (9), or malpresentation (9, 10) among survivors. There are two different causes for labor dystocia: mechanical obstructions (mechanical dystocia) and disruption of the contractions (functional dystocia) (20). In high income countries functional dystocia is the most common form, however, it is known that cancer treatment, and especially radiation therapy, has a degenerative effect on musculoskeletal development (21), which may lead to mechanical dystocia. These disruptions may also cause functional dystocia if the myometrium becomes affected; either by thinning of the uterus wall or by decreased uterine volume (22), and a US study found that the risk of labour dystocia and malpresentation among survivors of Wilms tumor correlated to the radiation dose (23, 24). An additional explanation to the increased risk of labour dystocia could be the elevated levels of endocrine complications among childhood cancer survivors (25). Injuries to the hypothalamus could affect the secretion of oxytocin, which plays an important role in labour. Labour dystocia is a major contributor to emergency CS and instrumental interventions (20), which was seen in the present study.

The risk of emergency CS was elevated in the present study, which could be dependent on the higher levels of IOL, labour dystocia and imminent fetal asphyxia. Previous research findings have been inconclusive, showing both increased risk of CS among survivors and no significant difference compared to controls (9, 10, 13, 26). In addition, survivors were more likely to undergo instrumental delivery by VE, and, as a consequence, higher levels of clitoral lacerations and anal sphincter injury. Contrary to our study, the British Childhood Cancer Survivor Study found that survivors were more likely to opt for elective CS (9), which was also found in a Finnish study (10). Our results indicate that women with a history of childhood or adolescent cancer have elevated levels of obstetric complications, and it is possible that these levels might have been lower if a higher proportion had undergone elective CS. However, it is also known that CS has several negative impacts on maternal and offspring's health, such as post-partum depression (27), post-partum hemorrhage (28) and infections (29). Therefore, in order to avoid necessary CS, healthcare professionals working within antenatal care and obstetrics should be aware of the risks and consider individual follow-up when needed.

Interestingly, the present study found that the survivors more often used epidural analgesia and local anesthesia, as well as opioids and sedatives during childbirth compared to the comparison group. A report from the he Children's Oncology Group show that childhood cancer survivors have an increased risk of anxiety and posttraumatic stress symptoms, especially if the survivors suffers from cancer-related pain (30), which could be an explanation to our findings. However, contradictory to that reasoning, the survivors in our study reported childbirth fear to a lower extent compared to those who had no cancer experience. An alternative explanation could be that cancer survivors have a greater experience in using medicines and thereby may have a lower threshold to use medication to alleviate pain during childbirth.

The present study findings indicate that pediatric cancer survivors have higher levels of adverse obstetric outcomes compared with those who were diagnosed during adolescence, as has been reported previously (10). The pediatric cancer survivors in our study had higher risk of IOL, primary and secondary labour dystocia, fetal asphyxia, instrumental delivery, emergency CS and that the offspring would be small for gestational age compared to the age-matched comparison group. These adverse outcomes could be dependent on receiving cancer treatment when still quite young, where toxic effects from chemotherapy and radiation therapy may lead to development of late adverse effects on the undeveloped body, such as uterine vascular insufficiency, reduced and/or uneven growth, or vascular and pulmonary

dysfunction (31, 32). The higher risk of adverse obstetric outcomes among pediatric cancer survivors calls for strict monitoring during pregnancy and childbirth.

The major strength was the population-based design where a five-year birth cohort was followed through register linkage. However, we did not have any treatment data available, and we could therefore not investigate how surgical interventions, or different levels of exposure of radiation therapy and chemotherapy impacted on the obstetric outcomes. By adjusting for maternal age, nicotine use and comorbidity we could control for factors known to have an impact on obstetric outcomes and the offspring's health. It was more common that survivors of childhood and adolescent cancer had a diagnosis of chronic renal disease and epilepsy compared to the comparison group, and the most likely explanation is that it was a consequence of their cancer and/or cancer treatment, and should therefore not have been adjusted for. However, the unadjusted and adjusted estimates was essentially similar and we do not believe that it had an impact on the result. Regrettably, due to a high degree of missing values, we could not adjust for maternal weight, which is a known factor for pre-eclampsia, IOL, CS and instrumental delivery (33). The sample consisted of 278 cancer survivors, which allowed computation of statistically trustworthy estimates. However, some sub-group analyses containing small samples presented large CI values, and therefore some caution is advised when interpreting the results. The study included individuals born between 1973 and 1977 and followed until first childbirth or December 31, 2012. As a consequence, the youngest participants included were 35 years old and it is possible that some who had not given birth at that time-point have had children later, which may have an impact on the results.

CONCLUSION

There is an increased risk of pregnancy and childbirth complications among female childhood and adolescent cancer survivors in connection with their first live birth compared with the age-matched comparison group. The higher levels of pre-eclampsia, malpresentation, IOL, labor dystocia and fetal asphyxia may be an explanation for the increased risk for VE, vaginal injuries and emergency CS. In the face of these findings, there is a need to optimize the pre- and perinatal care, especially among childhood cancer survivors.

REFERENCES

1. Chow EJ, Stratton KL, Leisenring WM, Oeffinger KC, Sklar CA, Donaldson SS, et al. Pregnancy after chemotherapy in male and female survivors of childhood cancer treated between 1970 and 1999: a report from the Childhood Cancer Survivor Study cohort. Lancet Oncol. 2016;17(5):567-76.

2. Madanat LM, Malila N, Dyba T, Hakulinen T, Sankila R, Boice JD, Jr., et al. Probability of parenthood after early onset cancer: a population-based study. Int J Cancer. 2008;123(12):2891-8.

3. Green DM, Kawashima T, Stovall M, Leisenring W, Sklar CA, Mertens AC, et al. Fertility of female survivors of childhood cancer: a report from the childhood cancer survivor study. J Clin Oncol. 2009;27(16):2677-85.

4. Green DM, Kawashima T, Stovall M, Leisenring W, Sklar CA, Mertens AC, et al. Fertility of male survivors of childhood cancer: a report from the Childhood Cancer Survivor Study. J Clin Oncol. 2010;28(2):332-9.

5. Hartman M, Liu J, Czene K, Miao H, Chia KS, Salim A, et al. Birth rates among female cancer survivors A Population-Based Cohort Study in Sweden. Cancer. 2013;119(10):1892-9.

6. Gunnes MW, Lie RT, Bjorge T, Ghaderi S, Ruud E, Syse A, et al. Reproduction and marriage among male survivors of cancer in childhood, adolescence and young adulthood: a national cohort study. Br J Cancer. 2016;114(3):348-56.

7. Armuand G, Skoog-Svanberg A, Bladh M, Sydsjo G. Reproductive Patterns Among Childhood and Adolescent Cancer Survivors in Sweden: A Population-Based Matched-Cohort Study. J Clin Oncol. 2017:JCO2016710582.

8. Anderson RA, Brewster DH, Wood R, Nowell S, Fischbacher C, Kelsey TW, et al. The impact of cancer on subsequent chance of pregnancy: a population-based analysis. Hum Reprod. 2018;33(7):1281-90.

9. Reulen RC, Bright CJ, Winter DL, Fidler MM, Wong K, Guha J, et al. Pregnancy and Labor Complications in Female Survivors of Childhood Cancer: The British Childhood Cancer Survivor Study. J Natl Cancer Inst. 2017;109(11).

10. Melin J, Heinavaara S, Malila N, Tiitinen A, Gissler M, Madanat-Harjuoja L. Adverse Obstetric Outcomes Among Early-Onset Cancer Survivors in Finland. Obstetrics and gynecology. 2015;126(4):803-10.

11. Kallen B, Finnstrom O, Nygren KG, Olausson PO. In vitro fertilization (IVF) in Sweden: infant outcome after different IVF fertilization methods. Fertil Steril. 2005;84(3):611-7.

12. Haggar FA, Pereira G, Preen D, Holman CD, Einarsdottir K. Adverse obstetric and perinatal outcomes following treatment of adolescent and young adult cancer: a population-based cohort study. PloS one. 2014;9(12):e113292.

13. Mueller BA, Chow EJ, Kamineni A, Daling JR, Fraser A, Wiggins CL, et al. Pregnancy outcomes in female childhood and adolescent cancer survivors: a linked cancer-birth registry analysis. Archives of pediatrics & adolescent medicine. 2009;163(10):879-86.

14. Clark H, Kurinczuk JJ, Lee AJ, Bhattacharya S. Obstetric outcomes in cancer survivors. Obstetrics and gynecology. 2007;110(4):849-54.

15. Melin J, Heinavaara S, Malila N, Tiitinen A, Gissler M, Madanat-Harjuoja L. Risk factors for preterm delivery among early onset cancer survivors: A Finnish register-based study. Int J Cancer. 2019;144(8):1954-61.

16. Pare E, Parry S, McElrath TF, Pucci D, Newton A, Lim KH. Clinical risk factors for preeclampsia in the 21st century. Obstetrics and gynecology. 2014;124(4):763-70.

17. Carneiro Teixeira JF, Maia-Lemos PDS, Cypriano MDS, Pellegrini Pisani L. Obesity in Survivors of Childhood Cancer: a Review. Pediatric endocrinology reviews : PER. 2017;15(1):33-9.

18. ACOG Practice Bulletin No. 107: Induction of labor. Obstetrics and gynecology. 2009;114(2 Pt 1):386-97.

19. Zenzmaier C, Leitner H, Brezinka C, Oberaigner W, Konig-Bachmann M. Maternal and neonatal outcomes after induction of labor: a population-based study. Arch Gynecol Obstet. 2017;295(5):1175-83.

20. Karacam Z, Walsh D, Bugg GJ. Evolving understanding and treatment of labour dystocia. European journal of obstetrics, gynecology, and reproductive biology. 2014;182:123-7.

21. Gawade PL, Hudson MM, Kaste SC, Neglia JP, Wasilewski-Masker K, Constine LS, et al. A systematic review of selected musculoskeletal late effects in survivors of childhood cancer. Current pediatric reviews. 2014;10(4):249-62.

22. Larsen EC, Schmiegelow K, Rechnitzer C, Loft A, Muller J, Andersen AN. Radiotherapy at a young age reduces uterine volume of childhood cancer survivors. Acta Obstet Gynecol Scand. 2004;83(1):96-102.

23. Green DM, Lange JM, Peabody EM, Grigorieva NN, Peterson SM, Kalapurakal JA, et al. Pregnancy outcome after treatment for Wilms tumor: a report from the national Wilms tumor long-term follow-up study. J Clin Oncol. 2010;28(17):2824-30.

24. Green DM, Peabody EM, Nan B, Peterson S, Kalapurakal JA, Breslow NE. Pregnancy outcome after treatment for Wilms tumor: a report from the National Wilms Tumor Study Group. J Clin Oncol. 2002;20(10):2506-13.

25. Chemaitilly W, Sklar CA. Endocrine complications in long-term survivors of childhood cancers. Endocr Relat Cancer. 2010;17(3):R141-59.

26. Shliakhtsitsava K, Romero SAD, Dewald SR, Su HI. Pregnancy and child health outcomes in pediatric and young adult leukemia and lymphoma survivors: a systematic review. Leuk Lymphoma. 2018;59(2):381-97.

27. Xu H, Ding Y, Ma Y, Xin X, Zhang D. Cesarean section and risk of postpartum depression: A meta-analysis. J Psychosom Res. 2017;97:118-26.

28. Bateman BT, Berman MF, Riley LE, Leffert LR. The epidemiology of postpartum hemorrhage in a large, nationwide sample of deliveries. Anesthesia and analgesia. 2010;110(5):1368-73.

29. Zuarez-Easton S, Zafran N, Garmi G, Salim R. Postcesarean wound infection: prevalence, impact, prevention, and management challenges. International journal of women's health. 2017;9:81-8.

30. Bitsko MJ, Cohen D, Dillon R, Harvey J, Krull K, Klosky JL. Psychosocial Late Effects in Pediatric Cancer Survivors: A Report From the Children's Oncology Group. Pediatr Blood Cancer. 2016;63(2):337-43.

31. Seehusen DA, Baird D, Bode D. Primary care of adult survivors of childhood cancer. Am Fam Physician. 2010;81(10):1250-5.

32. Oktem O, Kim SS, Selek U, Schatmann G, Urman B. Ovarian and Uterine Functions in Female Survivors of Childhood Cancers. Oncologist. 2017.

33. Triunfo S, Lanzone A. Impact of overweight and obesity on obstetric outcomes. J Endocrinol Invest. 2014;37(4):323-9.

LEGENDS

Table 1. Characteristics of cancer survivors and comparisons

Table 2. Diagnoses during pregnancy and childbirth

Table 3. Use of pain relieving methods during childbirth

Table 4. The health of the offspring

Table 1. Characteristics of cancer survivors and comparisons

	Survivors N=278	Comparisons N=829	*p*
Characteristics *	No. (%)	No. (%)	
Age at diagnosis			
Mean age (SD)	11.4 (6.2)	Not applicable	
	No. (%)	No. (%)	
Age group at diagnosis			
Childhood (<14 years)	169 (60.8)	Not applicable	
Adolescence (≥14-20 years)	109 (39.4)		
Educational level			0.580
9-10 years	10 (3.6)	33 (4.0)	
11-13 years	145 (52.2)	458 (55.3)	
≥14 years	123 (44.2)	337 (40.7)	
Relationship status			<0.001
Living with the father	244 (87.8)	767 (92.5)	
Other constellation	22 (7.9)	24 (2.9)	
Mean age at first live birth			<0.001
Mean age (SD)	27.6 (4.9)	32.1 (3.73)	
Min-Max	16-39	18-39	
Observation time to first live birth [a]			<0.001
Mean time (SD)	16.2 (7.7)	21.0 (7.3)	
Min-Max	0-35	3-35	
Comorbidities during pregnancy			
Repeated urinary tract infections	36 (12.9)	107 (12.9)	0.985
Chronic renal disease	7 (2.5)	4 (0.5)	0.003
Diabetes mellitus	1 (0.4)	6 (0.7)	0.508
Epilepsy	8 (2.9)	4 (0.5)	0.001
Lung disease/Asthma	14 (5.0)	71 (8.6)	0.056
Ulcerative colitis/Morbus Crohn	2 (0.7)	3 (0.4)	0.442
Chronic hypertension	1 (0.4)	1 (0.1)	0.417
Fertility problems			
Experience of fertility problems [b]	37 (13.3)	70 (8.4)	0.015
Use of ART [c]	11 (4.0)	17 (2.1)	0.080
Use of donor oocytes	2 (0.7)	1 (0.1)	0.094
Earlier spontaneous abortion	43 (15.5)	166 (20.0)	0.093
Prenatal diagnostics			
Chorionic Villus Sampling (CVS)	1 (0.4)	7 (0.8)	0.409
Amniocentesis	1 (0.4)	16 (1.9)	0.065
Nicotine use during pregnancy	28 (10.1)	80 (9.7)	0.838
Childbirth fear	2 (0.7)	23 (2.8)	0.046

* Percentages do not sum to total due to missing data; [a] Start at the 13th birthday or after the date of diagnosis/referent date. Followed until date of death, permanent emigration, first childbirth or December 31, 2012; [b] Having tried to conceive more than one year; [c] Assisted reproductive technique

TABLE 2

Table 2. Diagnoses during pregnancy and childbirth

	Survivors N=278	Comparisons N=829	Unadjusted	Adjusted†
	No. (%)	No. (%)	OR (95% CI)	OR (95% CI)
Diagnoses during pregnancy				
Diastasis symphysis pubis	3 (1.1)	21 (2.5)	0.42 (0.12-1.42)	0.47 (0.13-1.74)
Pregnancy hypertension	5 (1.8)	7 (0.8)	2.15 (0.68-6.83)	3.07 (0.85-11-12)
Preeclampsia	17 (6.1)	16 (1.9)	3.31 (1.65-6.64)*	3.46 (1.58-7.56)*
Gestational diabetes	4 (1.4)	9 (1.1)	1.33 (0.41-4.35)	1.30 (0.35-4.87)
Group B streptococcus positive	5 (1.8)	19 (2.3)	0.78 (0.29-2.11)	1.35 (0.47-3.91)
Anaemia	16 (5.8)	44 (5.3)	1.09 (0.61-2.00)	1.26 (0.66-2.42)
Twin pregnancy	4 (1.4)	14 (1.7)	0.85 (0.27-2.60)	1.07 (0.32-3.58)
Start of childbirth				
Elective caesarean section	13 (4.7)	84 (10.1)	0.44 (0.24-0.79)*	0.62 (0.33-1.17)
Spontaneous	228 (82.0)	654 (78.9)	1.22 (0.86-1.73)	0.85 (0.58-1.26)
Induction	37 (13.3)	91 (11.0)	1.25 (0.83-1.87)	1.66 (1.05-2.62)*
Labour complications				
Primary labour dystocia	12 (4.3)	15 (1.8)	2.45 (1.13-5.30)*	3.54 (1.51-8.34)*
Secondary labour dystocia	27 (9.7)	41 (4.9)	2.07 (1.25-3.43)*	2.43 (1.37-4.31)*
Imminent foetal asphyxia	30 (10.8)	47 (5.7)	2.01 (1.25-3.25)*	2.55 (1.49-4.39)*
Malpresentation of foetus	23 (8.3)	43 (5.2)	1.85 (1.09-3.15)*	2.02 (1.12-3.65)*
Vacuum extraction	26 (9.4)	45 (5.4)	1.80 (1.09-2.97)*	2.53 (1.44-4.47)*
Emergency caesarean section [i]	31 (11.2)	53 (6.4)	1.84 (1.15-2.93)*	2.34 (1.39-3.95)*
Lacerations and episiotomy				
Vaginal lacerations	104 (37.4)	316 (38.1)	0.97 (0.73-1.28)	1.34 (0.98-1.84)
Perineal lacerations	76 (27.3)	264 (31.8)	0.81 (0.60-1.09)	1.04 (0.74-1.45)
Clitoral lacerations	58 (20.9)	123 (14.8)	1.51 (1.07-2.14)*	2.18 (1.47-3.23)*
Anal sphincter injury	12 (4.3)	14 (1.7)	2.63 (1.20-5.75)*	2.76 (1.14-6.70)*
Episiotomy	21 (7.6)	34 (4.1)	1.91 (1.09-3.35)*	1.85 (0.98-3.49)
Postnatal complication				
Postpartum haemorrhage	23 (8.3)	64 (7.7)	1.08 (0.66-1.77)	1.31 (0.76-2.27)
Placental complication	11 (4.0)	31 (3.7)	1.06 (0.53-2.14)	1.18 (0.54-2.56)

OR = odds ratio; CI = confidence interval; * Statistically significant OR; † Adjusted for maternal age, nicotine use and comorbidity

Table 3. Use of pain relieving methods during childbirth *

	Survivors N=278	Comparisons N=829	*p*
	No. (%)	No. (%)	
No use of any pain relieving methods	2 (0.7)	27 (3.3)	0.022
No pharmacological method used	21 (7.6)	87(10.5)	0.153
Non-pharmacological methods			
Acupuncture	38 (13.7)	66 (8.0)	0.005
Warm tub bath	42 (15.1)	54 (6.5)	0.001
Sterile water injections	12 (4.3)	19 (2.3)	0.077
TENS [a]	19 (6.8)	46 (5.5)	0.430
Pharmacological methods			
Local			
Epidural analgesia	105 (37.8)	191 (23.0)	<0.001
Spinal anaesthesia	29 (10.4)	130 (15.7)	0.031
Local anaesthesia	73 (26.3)	125 (15.1)	0.001
Pudendal nerve block	9 (3.2)	20 (2.4)	0.456
Paracervical block anaesthesia	6 (2.2)	12 (1.4)	0.417
Systemic			
Nitrous oxide	203 (73.0)	574 (69.2)	0.233
Opioids	16 (5.8)	20 (2.4)	0.007
Sedatives	5 (1.8)	2 (0.2)	0.005
General anaesthesia	13 (4.7)	18 (2.2)	0.028

* Some women used more than one pain relieving method; [a] Transcutaneous electrical nerve stimulation

TABLE 4

Table 4. The health of the offspring

	Survivors N=278	Comparisons N=829	Unadjusted	Adjusted†
	No. (%)	No. (%)	OR (95% CI)	OR (95% CI)
Gestational age				
Preterm birth (<37 weeks)	45 (16.2)	29 (3.5)	2.03 (1.24-3.30)*	1.71 (0.98-2.98)
Postterm birth (>42 weeks)	3 (1.1)	1 (0.1)	0.99 (0.10-9.58)	0.61 (0.05-7.83)
Diagnoses				
Intrauterine growth restriction	4 (1.4)	14 (1.7)	0.85 (0.27-2-60)	1.10 (0.33-3.69)
Small for gestational age	11 (4.0)	20 (2.4)	1.66 (0.79-3.51)	2.25 (0.98-5.16)
Large for gestational age	0 (0.0)	13 (1.6)	0.41 (0.16-1.07)	0.54 (0.20-1.49)
Malformations	10 (3.6)	21 (2.5)	1.44 (0.67-3.09)	1.0 (0.42-2.39)
APGAR				
1 minute	30 (10.8)	68 (8.2)	1.35 (0.74-2.48)	1.06 (0.54-2.10)
5 minutes	11 (4.0)	23 (2.8)	2.75 (1.11-6.85)*	1.93 (0.68-5.45)
10 minutes	5 (1.8)	7 (0.8)	1.50 (0.27-825)	0.29 (0.06-1.07)
	mean (SD)	mean (SD)	Univariate ANOVA	Multivariate ANOVA
Measure				
Head circumference (cm)	34.6 (1.8)	35.0 (1.7)	-0.11 (-0.68- -0.20)*	-0.08 (-0.58- -0.06)*
Length (cm)	49.9 (2.6)	50.5 (2.6)	-0.10 (-0.94- -0.23)*	-0.09 (-0.95- -0.17)*
Weight (gram)	3356 (616)	3598 (585)	-0.17 (-322.64- -161.03)*	-0.16 (-316.13- -137.58)*

OR = odds ratio; CI = confidence interval; * Statistically significant OR; † Adjusted for maternal age, nicotine use and comorbidity. However, in the model for APGAR, only maternal age and comorbidity due to few observations regarding smoking and that all smokers had children with a low APGAR