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Clinical heart failure during pregnancy and delivery in a cohort of female childhood cancer survivors treated with anthracyclines

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ABSTRACT

The cumulative incidence of peripartum anthracycline-induced clinical heart failure (A-CHF) was evaluated in a cohort of 53 childhood cancer survivors who had delivered one or more children. None of them developed peripartum A-CHF (cumulative incidence 0%; 95% confidence interval (CI) 0–5.7%). The mean follow-up time after the first administration of anthracycline therapy was 20.3 years. They received a mean cumulative anthracycline dose of 267 mg/m^2. It is worth noticing that even 2 patients with A-CHF before pregnancy did not develop peripartum A-CHF. Since there were no cases of peripartum A-CHF in our cohort, it was not possible to evaluate associated risk factors.

In conclusion, this study demonstrates a low risk of developing peripartum A-CHF in childhood cancer survivors. However, more cohort studies with adequate power and long-term follow-up are needed to reliably evaluate the cumulative incidence of peripartum anthracycline-induced cardiotoxicity (both clinical and asymptomatic) and associated risk factors.

1. Introduction

Anthracyclines have gained widespread use in the treatment of numerous childhood malignancies: nearly 60% of children diagnosed with a malignancy receive anthracyclines. The introduction of anthracyclines has contributed to the improvement in survival rates of childhood cancer: from 30% in the 1960s to 70% currently.[1,2] As a result, a rapidly growing number of children will have survived childhood cancer. In the Netherlands, approximately 1 out of every 750–800 young adults has survived childhood cancer.[3]

Unfortunately, the use of anthracyclines is limited by the occurrence of cardiotoxicity. Several risk factors, like a higher cumulative anthracycline dose, a higher anthracycline peak dose, different anthracycline derivates, radiation therapy involving the heart region, female sex, younger age at diagnosis,

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black race, additional treatment with amsacrine, a longer follow-up time, and presence of trisomy 21, have been identified, although not conclusive in all studies.[4,5]

Cardiotoxicity can become manifest as either clinical heart failure[6] or asymptomatic cardiac dysfunction.[7] Both can not only develop during anthracycline therapy, but also years after the cessation of treatment.[8] In one of our earlier studies, the estimated risk of anthracycline-induced clinical heart failure (A-CHF) increased with time to 2% at 2 years and 5% at 15 years after the start of treatment.[9] The frequency of anthracycline-induced asymptomatic cardiac dysfunction has been reported to be up to 57%; also increasing with a longer follow-up period.[5,7,10] The risk of developing anthracycline-induced cardiotoxicity thus remains a lifelong threat. This is especially important in childhood cancer survivors who have a long life-expectancy after successful antineoplastic treatment.

An increasing number of female childhood cancer survivors reach the reproductive age and, although infertility occurs in such women,[11] a significant number of them become pregnant. Pregnancy and delivery are associated with cardiac stress.[12–14] The currently accepted estimate of incidence of peripartum heart failure in the normal population is approximately 1 case per 3000–4000 live births (0.03%).[15] Female childhood cancer survivors who have been treated with anthracyclines already have an increased gender-related risk to develop cardiotoxicity[16–18] and at the moment, it is unclear what the exact effect of the cardiac stress during pregnancy and delivery on the cardiac function of these patients will be. As described in case reports, it can have significant clinical implications for these women.[19,20]

The aim of this study was to evaluate the cumulative incidence of peripartum anthracycline-induced clinical heart failure and to identify the associated risk factors in a cohort of childhood cancer survivors treated with anthracyclines between 1966 and 1998.

2. Patients and methods

2.1. Patients

All female patients aged 17 years or older on 1st January, 2003 (or date of death) who survived for at least five years after the diagnosis of a childhood malignancy and were treated with anthracyclines at the Emma Children's Hospital/Academic Medical Center (EKZ/AMC) between 1966 and 1998 were included in this study. The patients were identified using the Registry of Childhood Cancer of the EKZ/AMC. This registry was established in 1966 and contains data on all children treated for childhood cancer in the EKZ/AMC with regard to diagnosis, treatment, and follow-up. According to the registry, 206 patients were eligible.

2.2. Treatment and follow-up data

In our hospital, patients who survived at least 5 years after the treatment of a childhood malignancy are seen at regular intervals at the Late Effects Outpatient Clinic (PLEK).[21] During these visits, information on pregnancy and delivery (including clinical heart failure) is obtained. Data were collected directly from the medical records. Attempts were made to establish the clinical status of patients lost-to-follow-up by sending a questionnaire to their general practitioners.

For each patient the following information was recorded: (1) date of birth, (2) type of malignancy and date of diagnosis, (3) treatment data (on anthracyclines, mitoxantrone, ifosfamide, cyclophosphamide, the cardioprotectant dexrazoxane, and concurrent radiotherapy involving the heart region (*i.e.* on the mediastinum, left part of the upper abdomen, left part of the thorax, thoracic spinal cord, and total body irradiation)), (4) last follow-up date, (5) date and cause of death, (6) signs and symptoms of clinical heart failure and, if that was the case, aetiology, time of occurrence, treatment and clinical outcome, and (7) characteristics of pregnancy and delivery. The cumulative overall anthracycline dose per meter squared was calculated as the sum of the doxorubicin dose, the daunorubicin dose, two thirds of the epirubicin dose and three times the idarubicin dose.[22–24]

2.3. Definition of clinical heart failure

A case of A-CHF was defined as congestive heart failure, not attributable to other known causes, such as direct medical effects of the tumour, valvular disease, septic shock, or renal failure. We defined congestive heart failure as the presence of the following clinical signs and symptoms: dyspnoea, pulmonary oedema, peripheral oedema, and/or exercise intolerance which were treated with anticongestive therapy. A cardiologist (W.K.) retrospectively confirmed the diagnosis in patients with cardiac events that may or may not have met this definition of clinical cardiotoxicity. The cardiologist was unaware of the cumulative anthracycline dose received by the patients. The clinical outcome of A-CHF was either 'death', 'alive with anticongestive treatment' or 'clinical recovery without current requirement for anticongestive therapy, but anticongestive treatment previously'. Depending on the time of onset, the A-CHF was classified as early A-CHF, *i.e.* during anthracycline chemotherapy or within the first year after the end of treatment, or as late A-CHF, *i.e.* more than 1 year after the completion of anthracycline chemotherapy.[8] A-CHF developing during pregnancy or within 5 months after delivery was classified as peripartum clinical heart failure. This definition is derived from the one used by the National Institutes of Health.[15]

2.4. Statistical analyses

Only patients who had delivered one or more children were included in the analyses.

The cumulative incidence of peripartum A-CHF was calculated as the number of women with peripartum clinical heart failure divided by the total number of pregnant women in the study group. The 95% confidence interval (CI) of the cumulative incidence of peripartum heart failure was calculated using the statistical program Confidence Interval Analysis.[25] If no cases of anthracycline-induced cardiotoxicity were identified, we used the 'Rule of Three' as described by Hanley and Lippman-Hand.[26]

3. Results

The study population included all 206 eligible patients. We succeeded in obtaining information on clinical status up to at least January 2003 (or date of death) for 185 patients (89.4% of the cohort). For the 21 other patients, we used the data of the last known follow-up date. At last contact 19 patients (9.2%) had died: 18 from tumour-related causes (12 from the primary tumour and 6 from a secondary tumour) and 1 cardiac death. The mean follow-up after the first administration of anthracyclines was 16.7 years (range 0.30–29.8 years). The mean age of the patients at the end of follow-up was 26.7 years. Fifty-seven of the 206 patients had been pregnant; 53 of these patients had delivered one or more children, 1 patient was 19 weeks pregnant at her latest follow-up visit, 3 patients had a medical abortion (not for cardiac reasons) and/or a spontaneous abortion. Only the patients who had delivered one or more children were included in the analyses. The clinical characteristics of the study population are listed in Table 1.

Table 1 – Clinical characteristics of 206 female childhood cancer survivors treated with anthracyclines

Characteristic	Pregnant (N = 53)		Not pregnant (N = 153)	
	N	%	N	%
Childhood cancer diagnosis				
Leukaemia	14	26	40	26
Lymphoma	16	30	40	26
Osteosarcoma	5	10	20	13
Ewing's sarcoma	10	19	13	9
Wilms' tumour	1	2	16	10
Others	7	13	24	16
Age at first dose of anthracycline (years)				
<2	1	2	7	5
2–6	7	13	45	29
7–11	21	40	41	27
12–16	22	41	57	37
>16	2	4	3	2
Cumulative dose of anthracycline (mg/m^2)				
⩽300	32	60	101	66
>300	20	38	52	34
Unknown	1	2	–	–
Mitoxantrone				
None	51	96	148	96
Any	2	4	5	4
Ifosfamide				
None	47	89	125	82
Any	6	11	28	18
Cyclophosphamide				
None	23	43	73	48
Any	30	57	80	52
Dexrazoxane				
None	53	100	145	95
Any	–	–	8	5
Radiotherapy involving the heart				
None	43	81	120	78
Any	10	19	33	22
A-CHF not related to pregnancy				
No	51	96	149	97
Yes	2	4	4	3

N, number; %, percentage; A-CHF, anthracycline-induced clinical heart failure.

3.1. Pregnant women

For the 53 patients included in the analyses, the mean age at the first administration of anthracycline therapy was 11.2 years (range 1.5–17.8 years).

The mean cumulative anthracycline dose was 267 mg/m^2 (range 60–552 mg/m^2): 36 of the childhood cancer survivors received only doxorubicin, 9 received only daunorubicin, 3 received only epirubicin, and 5 received a combination of different anthracycline derivates. None of the survivors received idarubicin. The exact cumulative dose of anthracyclines is unknown in 1 patient.

Different durations of anthracycline infusion were used: 50 patients received their anthracycline therapy by bolus and 3 by continuous infusion (over 20 min, over 1 h or over 4 h, respectively). Details of further treatment are shown in Table 1.

The mean follow-up time after the first administration of anthracycline therapy for all 53 patients was 20.3 years (range 5.8–28 years). The mean age of the patients at the end of the follow-up was 31.4 years (range 19.6–42.7 years). At last contact, 2 patients (3.8%) had died: 1 from a recurrence of her primary tumour and 1 as a result of a secondary malignancy (a maxillary sinus neoplasm).

3.2. Pregnancies and deliveries

In the 53 women who delivered one or more children, 100 pregnancies were identified: 13 spontaneous abortions (in 8 women; 1–4 each), 4 medical abortions (in 3 women; 1–2 each) and 83 deliveries.

Twenty of the 83 deliveries (24.1%) were caesarean deliveries, for 9 deliveries it was unclear if it was a vaginal or caesarean delivery. None of the caesarean sections were a result of cardiac reasons. The mean time from the first anthracycline administration to the first delivery was 15.3 years (range 4.1–26.4 years).

The total number of born children was 84 (including a pair of twins): 31 women (58.5%) had 1 child, 15 (28.3%) had 2 children, 5 (9.4%) had 3 children and 2 (3.8%) had 4 children. There were 37 boys (44%) and 42 girls (50%); of 5 children the gender was unknown. The gestational age at birth ranged from 26 to 42.6 weeks.

3.3. Anthracycline-induced clinical heart failure and risk factors

None of the 53 pregnant women developed peripartum A-CHF (0%; 95% CI 0–5.7%) during or after 83 pregnancies and deliveries (95% CI 0–3.6%). Since there were no cases of peripartum A-CHF in this cohort of patients, we were not able to adequately analyse the possible risk factors for peripartum A-CHF.

Two of the patients who became pregnant (3.8%) had been earlier diagnosed with A-CHF shortly after the end of anthracycline therapy. The characteristics of these patients are

Table 2 – Characteristics, treatment and follow-up of 2 patients with anthracycline-induced clinical heart failure before pregnancy

Pt	Tumour	Age at first dose of anthra (years)	Total dose of anthra (mg/m^2)	Mitoxantrone	Ifosfamide	Cyclophosphamide	RT involving the heart	Time to A-CHF (years)#	Outcome of A-CHF
1	NHL	10.3	420	No	No	Yes	No	0.02	No T
2	Ewing	13.6	480	No	No	Yes	No	0.30	T

Pt, patient; NHL, non-Hodgkin lymphoma; Ewing, Ewing sarcoma; anthra, anthracycline therapy; RT, radiotherapy; A-CHF, anthracycline-induced clinical heart failure; #, from last administration of anthracyclines; T, anticongestive therapy; no T, no anticongestive therapy at the time of last follow-up but anticongestive therapy previously.

shown in Table 2. After the diagnosis of A-CHF, patient 1 received anticongestive therapy for less than a year. After that her symptoms of A-CHF had disappeared and her left ventricular shortening fraction (LVSF) returned to normal with values of at least 34%. She had a vaginal delivery after 40.6 weeks of pregnancy 13.9 years after the diagnosis of A-CHF. She developed no signs of A-CHF. No echocardiogram was performed after the pregnancy. After patient 2 was diagnosed with A-CHF, she was initially treated with anticongestive therapy. When her symptoms disappeared the medication was terminated after 3.5 years, even though her LVSF was abnormal with values of 27% or less. During her pregnancy and delivery, she was free of medication. She had a vaginal delivery after 40 weeks of pregnancy 14.5 years after the diagnosis of A-CHF. When 2.5 years after the delivery, the symptoms of A-CHF returned, anticongestive therapy was initiated again. At the moment, her symptoms are stable, as is her LVSF (at 17%).

4. Discussion

This study demonstrates a low risk of developing peripartum A-CHF in childhood cancer survivors. None of the 53 patients who were treated with anthracyclines for childhood cancer developed peripartum A-CHF. Also, it is worth noticing that 2 of the 53 women included in this study developed A-CHF shortly after the end of anthracycline therapy and that neither of them developed any peripartum cardiac problems. Although this is an encouraging finding, it is important to realise that because of the low power of this study the real cumulative incidence of peripartum A-CHF can be as high as 5.7% (*i.e.* the upper limit of the 95% CI). This is considerably higher than the currently accepted estimate of incidence of peripartum heart failure in the normal population, which is approximately 1 case per 3000–4000 live births (0.03%).[15]

It was not possible to determine if patients were advised not to become pregnant. For example, it could be possible that patients in our cohort of childhood cancer survivors who were treated with higher cumulative anthracycline doses were advised not to become pregnant in order to avoid cardiac problems. However, this possibility is not supported by the cumulative anthracycline dose received by patients who did and did not become pregnant. The mean cumulative anthracycline dose of patients who were not pregnant was 282 mg/m^2 (range 40–670 mg/m^2) and this is not significantly different from the cumulative anthracycline dose received by the pregnant women in this study (mean 267 mg/m^2; range 60–552 mg/m^2).

This study could not evaluate the incidence of peripartum anthracycline-induced asymptomatic cardiac dysfunction. In our institution, childhood cancer survivors treated with anthracyclines do not routinely undergo an echocardiographic evaluation of their LVSF around pregnancy and delivery. As a result, none of the patients in our study group had an echocardiogram before and/or during the pregnancy and within 5 months after the delivery. Therefore, it was also not possible to evaluate the influence of pregnancy and delivery on the increase in asymptomatic cardiac dysfunction reported with longer follow-up.[7,10]

Until now, only Bar and colleagues[27] have evaluated pregnancy-related anthracycline-induced asymptomatic cardiac dysfunction in childhood cancer survivors. The study population consisted of 37 women (63 deliveries) of which 10 (27%) developed anthracycline-induced asymptomatic cardiac dysfunction (defined as a LVSF of less than 30% or a drop in LVSF units of 10% or more) after pregnancy. This finding is not evaluated in relation to the development of clinical events later on. Also, although all patients in this study did have an echocardiographic follow-up of LVSF, the power of this study is still low. Furthermore, it is not clear if this study evaluated a complete cohort of patients and as a result selection bias cannot be ruled out.

More cohort studies with a high number of pregnant patients and long-term follow-up are needed to reliably evaluate the cumulative incidence of peripartum anthracycline-induced cardiotoxicity (both clinical and asymptomatic, as measured by, for example, regular echocardiograms) and associated risk factors. Preferably, these new studies will also evaluate the long-term difference in cardiac function between anthracycline-treated childhood cancer survivors who have been pregnant and those who have not been pregnant. As more data become available, clinicians will be able to make well-informed decisions about adequate follow-up protocols for pregnant childhood cancer survivors who have been treated with anthracyclines. Although the 2 patients who were diagnosed with A-CHF shortly after the end of anthracycline therapy did not develop any peripartum cardiac problems, it is known that pregnancy in women with pre-existing heart disease can be associated with significant cardiac complications. We recommend careful monitoring of patients with prior A-CHF around their pregnancy.[28]

In conclusion, this is the first study to investigate the cumulative incidence of peripartum A-CHF in a complete cohort of patients. Although the risk of developing peripartum A-CHF in childhood cancer survivors is probably higher than

in the normal population, none of the patients in our cohort developed peripartum A-CHF.

Conflict of interest statement

None of the authors have competing interests.

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