Obstetric outcome and maternal survival in patients diagnosed with Hodgkin Lymphoma during pregnancy: a retrospective cohort study of 134 cases of the International Network of Cancer, Infertility and Pregnancy

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Abstract

Background

The purpose of this study was to investigate obstetric and maternal outcome of pregnant patients with Hodgkin lymphoma (HL).

Methods

Clinical data of pregnant patients diagnosed with HL were registered by the International Network on Cancer, Infertility and Pregnancy (INCIP). For survival analysis of patients that received ABVD-based treatment between 1997 and 2018, matched non-pregnant controls were selected based on stage and prognostic score at diagnosis.

Findings

The majority of the 134 included patients were diagnosed with early stage HL (75%) and nodular sclerosis subtype (81%). The median gestational age at diagnosis was 20 weeks (range 3–37). 58% of patients initiated with antenatal treatment and over the years chemotherapy was increasingly prescribed during pregnancy. 90% of pregnancies ended in a live birth. 19% of neonates were small for gestational age and, customised birthweight percentiles were lower in neonates prenatally exposed to chemotherapy compared to non-exposed neonates ($p=0.035$). Progression-free survival (PFS) and overall survival (OS) of pregnant patients was not significantly different from non-pregnant controls. Five-year PFS and OS for early stage HL was 82.5% and 97.3% for 62 pregnant patients and 88.2% and 98.4% for 142 non-pregnant patients, respectively. Subgroup analysis of patients that initiated chemotherapy during pregnancy or had a pregnancy-related delay to initiate treatment was re-assuring. For advanced stage HL 5-year PFS and OS survival was 90.9% and 100% for 15 pregnant patients and 74.0% and 96.2% for 69 corresponding controls, respectively. Low numbers did not allow solid conclusions.

Interpretation

The increasing trend to treat HL during pregnancy might impact foetal growth, whereas the maternal overall survival remains intact. Our re-assuring results can only be consolidated if management during pregnancy adheres as much as possible to standard protocols.

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Introduction

Following the trend of increased age at first childbirth, over time more patients will be diagnosed with cancer during pregnancy.¹ The type of cancers diagnosed during pregnancy reflects the distribution of those found in women of reproductive age, the top five being breast cancer, thyroid cancer, lymphoma, melanoma, and cervical cancer.² Hodgkin lymphoma (HL) represents the most common haematological malignancy during pregnancy, with an estimated incidence between 5 and 8 per 100,000 live births.^{3, 4}

Outside pregnancy, HL treatment is based on disease stage and the presence of clinical risk factors. In the present era, patients are treated with polychemotherapy (ABVD (doxorubicin, bleomycin, vinblastine, dacarbazine)) or Escalated BEACOPP (bleomycin, etoposide, adriamycin, cyclophosphamide, vincristine, procarbazine, prednisone)), combined with radiotherapy on indication for early stage disease.

Limited studies are available to guide staging, treatment and response evaluation of HL during pregnancy. El-Messidi published the largest cohort on 638 cases, revealing an increased risk of preterm delivery, postpartum blood transfusion and venous thrombosis but overall comparable short-term maternal and neonatal morbidity and mortality in comparison to 7,916,388 controls.⁴ In contrast, a Danish nationwide cohort study on 292 births showed reassuring birth outcomes without increased risk of preterm delivery, stillbirth or low birthweight (<2500 gram) at term.⁸ Few retrospective series report on antenatal treatment strategies in detail. Most series report on the use of ABVD during pregnancy, whereas experience with BEACOPP during pregnancy is limited.^{9, 10} Some authors suggest deferral of treatment until after delivery to minimise foetal risks in early stage HL.⁹ However, in symptomatic patients or advanced HL, immediate treatment is often indicated. Increased awareness of the feasibility of chemotherapy during pregnancy resulted in more patients receiving anticancer drugs.¹¹

To date, there is no indication that a pregnancy might impact the course of Hodgkin Lymphoma. Relatively small series evaluating survival in pregnant patients diagnosed with HL reveal a maternal outcome equal to the non-pregnant population, however do not report on management during pregnancy in detail.¹³⁻¹⁵ Survival of patients that initiate treatment during pregnancy is of great interest because gestational physiological changes (eg. higher plasma volume and distribution volume, increased glomerular infiltration, altered hepatic metabolism) potentially affect pharmacokinetics, resulting in a lower plasma-drug exposure.¹² Whether this chemodilution affects the efficacy of chemotherapy remains questioned. Also, it is unclear whether pregnancy-induced adaptations in management (eg. deferral of treatment until the second trimester of pregnancy or postpartum) impact maternal survival.

Here, we report the results of a multicentre collaboration that retrospectively collected clinical data of 134 pregnant patients with HL. The aim of this study is to assess oncological management and obstetric outcome when HL is diagnosed during pregnancy. Also, the oncological maternal outcome is studied by assessing PFS and OS patients diagnosed with classical HL during pregnancy and treated with ABVD (initiated during or after pregnancy) in comparison to stage and prognostic score matched controls.

Methods

Study design and participants

The International Network on Cancer, Infertility and Pregnancy (INCIP) study (www.cancerinpregnancy.org), supported by the European society of Gynaecological Oncology (ESGO), launched an international registry for cancers diagnosed in association with pregnancy. Doctors affiliated to the INCIP voluntary report patients who are treated in tertiary centres. Ethical approval was obtained from the participating centres when indicated. Only patients with a diagnosis of HL during pregnancy and known management during pregnancy and pregnancy outcome were included for analysis. In total, 17 academic centres from 11 different countries (in order of numbers of inclusion: the USA, Russia, Belgium, the Netherlands, Mexico, Italy, Czech republic, Israel, United Kingdom, Greece ,and Denmark) registered 151 patients with a diagnosis of pregnancy-associated HL between 1969 and 2018. After excluding 17 patients with a postnatal diagnosis, relapse of HL during pregnancy or incomplete data, 134 patients were eligible for analysis. A recent INCIP study on oncological management and obstetric outcome of 1170 patients with a cancer diagnosis during pregnancy did report on 65 HL patients included in this cohort, however the study design did not allow cancer-specific analysis.¹¹

Procedures

Clinical data regarding oncological diagnosis, treatment, obstetric outcome, neonatal outcome and maternal survival were collected. Missing data (yearly follow-up, histological subtype, details on recurrence) were requested from INCIP members prior to the study. All patients were staged and treated according to the local protocols of the participating centres. A patient was considered to have a recurrence of HL if this was registered with details on the location of relapse based on biopsies or imaging. Due to the retrospective study design predefined definitions of remissions, recurrence or follow-up after treatment were not possible. Early and advanced stage HL was defined according to the Ann Arbor staging system as early stage (stage I-II) and advanced stage (stage III-IV).¹⁶ Prognostic scores were defined by the criteria of the European Organization for Research and

Treatment of Cancer (EORTC) for early stage and the International Prognostic Score (IPS) for advanced stage HL.^{17, 18}

Twin pregnancies were excluded for analysis of obstetric and neonatal outcomes and stillbirths were not included for neonatal observations. We compared the outcome of chemotherapy-exposed neonates with non-exposed neonates. As treatment with only radiation therapy is no longer the standard for HL and with the increasing trend to treat with chemotherapy during pregnancy, we believe this approach is most relevant for current practice. Small for gestational age (SGA) for singletons was defined as a birthweight below the 10th percentile corrected for gestational age, neonatal sex, maternal height, maternal weight, ethnicity and parity (GROW v.8.0.2, www.gestation.net). Congenital malformations were assessed according to Eurocat.¹⁹

To study the effect of pregnancy on maternal outcome, survival analysis was restricted to patients with similar tumour (classical HL) and treatment (ABVD-based) characteristics. We identified young (≤ 41 years) non-pregnant controls who were matched for stage and prognostic score at diagnosis with pregnant patients (patients with a termination of pregnancy or miscarriage were excluded). The lack of uniform international definitions and a likely underreporting because of retrospective or missing data, did not allow us to match for B symptoms or bulky disease. The first registered pregnant INCIP patient that received ABVD was treated in 1997. Controls were selected based on their presentation in the same time period as pregnant patients (between 1997 and 2018) in the outpatient clinic of the department of haematology and oncology at the University Hospitals of Leuven (Belgium), the Erasmus MC Cancer Institute in Rotterdam and the University Medical Centres in Groningen (the Netherlands).

Statistical analysis

PFS was calculated from the time of lymphoma diagnosis to the time of disease relapse/progression or death. OS was measured from the date of lymphoma diagnosis to the date of death of any cause. Kaplan Meier estimates were used for constructing survival curves. Matching was performed selecting for every case as many as possible controls based on stage at diagnosis (I-II versus III-IV) and prognostic score (favourable versus non-favourable for early stage disease and score 0 or 1 versus 2 versus 3, 4 or 5 for advanced stage). The statistical comparison between pregnant and non-pregnant patients was performed based on a Cox regression model using a robust sandwich estimate of Lin and Wei (1989) to account for clustering due to patient matching. Correction for age was performed by including age as a covariate in the model.

We used the Fisher exact test to compare groups on binary variables and the independent t test or Mann Withney U test, as appropriate for continuous variables. Two sided p values of 0.05 or less were considered significant. Data were collected in a Microsoft SQL Server Database. Analysis was performed with IBM SPSS Statistics version 21 and SAS software (version 9.4 of the SAS System for Windows).

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Results

Disease characteristics

Baseline characteristics for 134 eligible patients with a diagnosis of HL during pregnancy are shown in table 1. Median age at diagnosis was 27 years (range 16-40). Nodular sclerosis HL was the most common histological subtype (81%). Most women were diagnosed with early stage HL (n= 101, 75%). The majority of patients were nulliparous (65%) and had no B symptoms at diagnosis (55%).

Gestational data and management

Median gestational age at diagnosis was 20 weeks (range 3–37). 61% of patients were diagnosed in the second trimester of pregnancy. Ten patients, diagnosed in the first trimester or early second trimester opted for a termination of pregnancy in order to initiate immediate treatment, four of whom had advanced stage disease.

The management of HL according to trimester of pregnancy at diagnosis is shown in figure 1. Antenatal chemotherapy was initiated in 72 patients, at a median gestational age of 22 weeks (range 10-35). ABVD (at standard doses) was the most common regimen administered during pregnancy (92%) (Supplementary Table 1). Over time, the proportion of patients commencing chemotherapy during pregnancy increased, while the proportion in whom therapy was deferred until after delivery decreased (figure 2).

Obstetric outcome and complications

In total, 120 pregnancies ended in a live birth (90%). One foetus with a congenital syndrome (exact diagnosis not registered) deceased at 24 weeks of gestation, soon after administration of ABVD during pregnancy. In one patient a stillbirth with a large placental hematoma was detected during routine control at 31 weeks of gestation, after 3 cycles of ABVD. Two patients presented with a miscarriage detected in the early second trimester, before the initiation of treatment for HL. Table 2 presents the obstetric outcome of all 117 singleton pregnancies. Median gestational age at delivery was 37 weeks (range 29-40). 64% of all deliveries occurring before 37 weeks of gestation were planned for oncological reasons. Patients receiving antenatal therapy had more obstetric complications, the most common being preterm contractions and preterm rupture of membranes (Supplementary Table 3, 4). Preterm contractions followed by preterm delivery (range 29-36) were reported in eight patient receiving chemotherapy during pregnancy. Only one patient with expectant management after a diagnosis of HL at 24 weeks gestation, had a preterm spontaneous delivery at 34 weeks.

Neonatal outcome and complications

In total, 123 children were born out of 122 ongoing pregnancies (two stillbirths, three twin pregnancies and 117 singletons). 33 neonates (30%) had a birthweight below 2500 gram and 21 neonates (19%) were small for gestational age. The absolute birthweight of 69 neonates prenatally exposed to chemotherapy did not differ from non-exposed neonates (Table 3). Also, the incidence of SGA neonates was not significantly different (22% chemo-exposed versus 16% non-chemo exposed, $p=0.455$). However, the distribution of customised birthweight percentiles differed significantly between both groups ($p=0.035$, see also Supplementary Figure 1).

Four children (3%) had a major congenital anomaly at birth (two cases of syndactyly, one atrial septal defect and one congenital syndrome, see Supplementary Table 5). In addition, four children (3%) had minor physical abnormalities.

Myelosuppression (leukopenia, anaemia) were reported in two foetuses, born one and two weeks after the last administration of chemotherapy during pregnancy (Supplementary Table 6). In total 32 children (31%) were hospitalised at birth and prematurity was the main reason (21 children, 66%). Other reasons for admission were dysmaturity (5 children, 16%) or observation (6 children, 19%). Two twin pregnancies ended by caesarean section at 29 weeks of gestational age due to spontaneous preterm labour, within two weeks following administration of chemotherapy. Another patient delivered of twins at 35 weeks, following induction of labour in order to start treatment. The twins were healthy at birth but hospitalised in the neonatal intensive care unit (NICU) for prematurity.

Maternal outcome

In total 211 matched control patients were selected for 77 pregnant patients that received ABVD-based treatment for classical HL. (Supplementary Table 7). Six cases with early stage HL were excluded because no matched controls were found. Six included cases were only matched for (early) stage and not for prognostic score as this was not reported. These cases had excellent survival without any events. All survival analysis were corrected for age. Diagnostic year and use of radiation therapy in primary treatment did not differ between pregnant and non-pregnant cases (Supplementary Table 8).

The median follow-up of pregnant patients was 54.5 months. Five-year PFS and five-year OS for early stage HL, was 82.6% and 97.3% for pregnant patients and 88.2% and 98.4% for non-pregnant controls, respectively ($p=0.129$ (PFS) and $p=0.534$ (OS), Figure 3A and B). For advanced stage HL, 5-year PFS and OS survival was excellent, respectively 90.9% and 100% for 15 pregnant patients and 74.0% and 96.2% for 69 corresponding controls ($p=0.334$ (PFS); $p=0.1461$ (OS)). Because of low numbers, further subgroup analysis for advanced stage disease were not performed. Subgroup analysis of 45 early stage HL pregnant patients that initiated chemotherapy during pregnancy revealed similar survival compared to non-pregnant controls (78.2% vs 87.8% for PFS $p=0.0886$) and 96.2% vs 97.7% for OS ($p=0.854$), see Figure 3C and D). Early stage HL patients ($n=21$) with a delay in initiation of treatment attributed to pregnancy, arbitrary defined as more than 35 days since diagnosis, had no differences in survival compared to their matched controls ($n=33$) (88.0% vs 90.9% for PFS ($p=0.477$) and no events in both groups for OS) (Supplementary Figure 2). In this group, more than half of patients were diagnosed in late second or third trimester of pregnancy with stage I-II HL and initiated therapy after (mostly planned and term) delivery whereas ten patients (30%) were diagnosed very early in pregnancy and had a delay to initiate chemotherapy in the second trimester of pregnancy.

Discussion

Here, we report the obstetric and maternal outcome of 134 pregnant patients diagnosed with HL between 1969 and 2018. Over the years there is an increased trend to treat during pregnancy, which put the foetus at risk for low birthweight percentile. For early stage disease, survival of pregnant patients was not significantly different from non-pregnant controls. Although the low numbers do not allow a solid conclusion on survival of pregnant patients with advanced stages HL, survival in this subgroup was excellent. To the best of our knowledge this is the largest series of HL during pregnancy reporting on obstetric outcome and maternal survival with detailed information on treatment modalities.

The majority of pregnant patients in this series presented as early stage HL. Although a suboptimal staging during pregnancy is plausible, other series equally reported a higher prevalence of early stage disease, which is

comparable to the distribution in the non-pregnant population and reflects the slow-growing nature of the tumour in most patients.^{13, 14}

Data suggest that the use of ABVD during the second and third trimester is feasible.⁹ Reflecting the limited experience with escalated BEACOPP during pregnancy, this regimen was initiated during pregnancy in only one patient and postpartum in two patients in this series. Over time more patients initiated chemotherapy during pregnancy with a deferral of radiotherapy until after delivery. Data on radiation during pregnancy are based on small series, but irradiation of supra-diaphragmatic disease appear to incorporate a low risk for the foetus (ref). While the option of radiotherapy during pregnancy can be considered in well selected cases, treatment for HL is initially chemotherapy-based and it is not anymore the standard of care to initiate primary radiotherapy.^{5, 6}

The overall obstetric complication rate was higher in patients receiving antenatal treatment compared to patients without antenatal treatment, mostly due to the higher incidence of preterm contractions. Another series on 44 pregnant patients with chemotherapy for early stage HL during pregnancy reported 22% preterm delivery, but no other obstetric complications.¹⁰ A breast cancer series also found a higher obstetric complication rate in patients receiving antenatal cancer treatment compared to patients without antenatal treatment, but similar to this HL series, no specific complication was significantly more prevalent in the exposed group.²¹ In one cohort study caesarean section or induction of labour were considered as complications and were more common in the non-exposed group.¹³ In our cohort, this prevalence were comparable between patients with and without antenatal treatment. However, the caesarean section rate (35%) was higher compared to the recently reported rates in Western Europe (26.9%), North America (32%) and worldwide (21.1%).²² More than one third of patients had an induction of labour, which is also higher compared to the international reported data (9.6 to 25%).²³

As customised birth weight percentiles were significantly lower for neonates prenatally exposed to chemotherapy compared to non-exposed neonates, data of this series indicate that antenatal chemotherapy might impact foetal growth, as already demonstrated in former studies (Table 3).^{11, 24} Other studies on HL focused on the absolute birth weights of neonates, not correcting for gestational age at delivery, or were too small to draw conclusions.^{8, 13}

However, in a cancer population not only cytotoxic drugs that cross the placenta, but also malnutrition, poor maternal health and maternal stress might explain impaired foetal growth. The high overall incidence of SGA of 19% in this series and the finding that birth weight percentiles were not symmetrically distributed for both exposed and non-exposed neonates (eg. left-shifted), support a multifactorial cause. In addition, pregnant patients that initiated chemotherapy were significantly more diagnosed in early pregnancy with longer intervals between diagnosis and delivery, compared to patients that initiated treatment after delivery (Table 3). These patients are

thus subject to a longer antenatal period of cancer-related stress and symptom, which might also contribute to impaired foetal growth. Furthermore, sub-analysis by linear regression on duration of treatment during pregnancy and customised birthweight percentiles did reveal an association in this series (preliminary data not shown). We did not find an increased rate of neonatal morbidity in this series, consistent with prior data.^{8, 10, 13} The major congenital malformation rate was comparable to that of the general population, with a background risk of 2.8 to 6.9% for major malformations and 6.5 to 35.8% for minor abnormalities.^{25, 26}

In the literature of the non-pregnant population 5 year PFS ranges between 86.4 and 94.2% and 5 year OS between 96.0 and 98.8% for early stage HL.²⁷ The survival of patients with advanced stage HL is inferior with reported rates of 78% 5 years PFS and 90% 5 year OS.²⁸ Thus, survival rates from the non-pregnant matched control group in this study were within expectations. Maternal outcomes for early and advanced stage HL in this series were a 5-year PFS rate of 82.5 and 90.9% and an OS rate of 97.3 and 100%, respectively. Most previous reports on maternal outcome after HL do not distinct between early and advanced stage HL, but overall similar survival rates were found.^{14, 15} One cohort study of 50 patients revealed a 3-year PFS and OS of 85% and 97%, respectively, comparable to this series.¹³ A recent report on 44 patients diagnosed with early stage HL during pregnancy with median follow-up of 11.5 years revealed an OS of 95%, whereas our series found an OS of 98% at 10 years in this subgroup.¹⁰ Small differences between the studies might be explained by different adverse prognostic factors of HL, such as presence or absence of B symptoms and bulky disease.^{13, 14}

Based on gestational changes, there are some reasons to assume a plausible suboptimal cancer treatment in pregnant patients. An important, yet underinvestigated, concern is the gestation-related lower plasma-drug exposure.¹² Currently it is recommended to define treatment dosages based on actual body weight in pregnant patients, with (usually) increasing dosages as pregnancy advances.¹² Our data on OS survival show that, if HL relapse occurs after primary treatment with chemotherapy during pregnancy, salvage treatment (including high dose chemotherapy followed by autologous stem cell transplantation) remains an effective option.

Another concern are the pregnancy-related treatment adaptations, such as deferral of cytotoxic treatment until the second trimester of pregnancy or until after delivery. In this series, survival of 21 pregnant patients with a delayed initiation of treatment for HL was similar to 33 corresponding controls. This supports previous suggestions that in selected patients delivery can be expedited and therapy started postpartum with little delay, bridging with steroids or vinblastine if appropriate.^{9, 13, 29} This strategy might be an option in particular cases with asymptomatic patients diagnosed in the early third trimester of pregnancy in order to enable a term delivery, as prematurity is the primordial reason for impaired cognitive outcome in children prenatally exposed to cancer or cancer treatment.³⁰

Our survival data should be interpreted carefully as relapses after pregnancy were not always reported to be histologically confirmed as a relapse of classical HL. Also ,in one case the distinction between recurrence or residual disease based on a PET scan after pregnancy was difficult to assess because of the inferior imaging technique (CT scan) used for staging during pregnancy. She was considered to have a relapse and aggressive treatment was initiated, in order not to take the risk of undertreatment. Given the risk of late treatment-related toxicity, over the years there has been an important evolution towards tailoring treatment according to treatment response assessed by interim Positron Emission Tomography (PET) scan results. The introduction of detectable nodal irradiation techniques allow a better control of tumour sites with less adverse events compared to extended field irradiation. Obviously, during pregnancy concerns on foetal radiation exposure limit imaging and radiation treatment options, which might lead to inferior staging and response evaluation.⁷ This is an important limitation of this cohort as very likely a substantial amount of non-pregnant patients was managed according to this novel approach.

An important strength of this study is the large cohort with detailed information on treatment modalities during pregnancy. As ABVD-based treatment for HL is still considered the standard treatment, the wide period of inclusion for survival analysis is justified. By comparing survival within an international group, differences in staging and treatment modalities influencing survival are possible. However, all patients were treated in tertiary centres with high standards of care. An important limitation of this study is its retrospective design, unavoidably resulting in missing data (eg. bulky disease, B symptoms). The international character of the study inevitably results in selection bias. For follow-up we could only rely on the quality of registered data. Control patients were selected from three University hospitals with available registries and unfortunately country-based selection was not possible as most participating centres did not keep records routinely. Furthermore, underreporting of minor obstetric or neonatal complications cannot be excluded. There is an increasing trend to treat with chemotherapy during pregnancy for HL. If it is indicated for maternal reasons, this approach can be considered and appears oncological safe, with no impact on maternal overall survival. Obstetric monitoring is indicated because of the risk of impaired foetal growth. In well selected cases (eg. asymptomatic early stage HL) deferral of treatment until after delivery may be an option. Further prospective studies are needed to define the efficacy of chemotherapy during pregnancy. Specialists with an interest in cancer and pregnancy are encouraged to participate in the worldwide registry of INCIP.

Research in context

Evidence before this study

Hodgkin lymphoma (HL) is the most common haematological malignancy diagnosed during pregnancy and the first-line treatment is chemotherapy-based. Initiation of chemotherapy during pregnancy might endanger obstetric and neonatal outcome. As gestation alters pharmacokinetics of drugs, with a lower area under the curve (AUC) and a lower peak plasma concentration, the efficacy of cytotoxic drugs during pregnancy remains questioned. We searched PubMed on August 1, 2018, for articles on cohorts of patients with HL during pregnancy, published between Jan 1, 1990, and Oct 31, 2018, using the following keywords: “pregnancy”, “cancer”, “hodgkin”, “lymphoma”, “obstetric outcome”, and “maternal outcome”. The search was restricted to publications in English. We found six studies reporting on obstetric and/or maternal outcome of HL during pregnancy with a sample size ranging from 31 to 638. All studies had a retrospective design. The two large nationwide studies investigating the obstetric outcome of 292 and 638 pregnant HL patients, did not provide information on treatment modalities during pregnancy. Only four of the selected studies reported on long-term maternal survival, with a reported maximum median follow-up of 120.4 months. One report limited survival analysis to early stage HL, whereas the other three studies did not distinct between early and advanced stage HL. There was only one study that used non-pregnant control patients for survival analysis, matched by age, stage, presence or absence of B symptoms and year of diagnosis (Lishner et al, 1992). Nevertheless, this study was small, reporting on 33 pregnant patients and 67 controls, included also patients with a postnatal cancer diagnosis and only six patients with chemotherapy during pregnancy. In all studies reporting on maternal survival, no further analysis of subgroups of patients with chemotherapy during pregnancy or deferred treatment was performed.

Added value of the study

To our knowledge, this study is the largest cohort to date that reports on the obstetric outcome and maternal survival of patients with HL diagnosis during pregnancy, with detailed information on management during pregnancy and neonatal outcome. The obstetric outcome of 65 out of 134 patients was previously reported in our multicentre cohort study on 1170 patients with a cancer diagnosis during pregnancy where we focused on the evolution of oncological management and obstetric outcome for cancers, without detailed cancer-specific information (de Haan et al, 2018). The study revealed an increasing trend of chemotherapy for HL during pregnancy, which is associated with lower customised birth weight percentiles. Progression-free and overall survival did not seem to be affected by pregnancy. Nevertheless, for early stage HL there was a trend of inferior

384 progression-free survival compared to non-pregnant controls, and this was even more apparent for the subgroup
385 that initiated chemotherapy during pregnancy. However, overall survival was similar to non-pregnant controls,
386 which confirms the efficacy of salvage treatment. Deferral of treatment until after delivery in selected cases did
387 not seem to impact survival.

388 389 **Implications of all the available evidence**

390 The increasing awareness of the feasibility of chemotherapy during pregnancy results in more patients initiating
391 treatment during pregnancy and more neonates at risk for small for gestational age. Continuous surveillance of the
392 general health of these exposed neonates is warranted as evidence of long-term follow-up (including cancer risk
393 and fertility) of these children is still limited. Chemotherapy for HL during pregnancy does not seem to affect
394 maternal survival and in selected cases (asymptomatic early stage HL) deferral of treatment until after delivery
395 might be an option. However, as gestation-related pharmacokinetic changes might affect drug exposure and
396 efficacy, further prospective studies on maternal survival in this population are indicated. The rarity of cancer and
397 pregnancy imposes international research, of which the INCIP project is a unique concept
398 (www.cancerinpregnancy.org).

Contributors

FA designed the study. CM, DD and SW performed a literature search on Hodgkin Lymphoma during pregnancy. All authors contributed to data collection; Pregnant cases were registered by CM, EC, ES, ACG, MMG, MH, NO, KVC, AOL, EP, LVD, IA and FA. CM, DD, PL, MB, PV, SW and FA contributed to the selection of non-pregnant control patients. CM, DD, KVC, SW and FA gathered and interpreted the data. CM, DD and AL analysed the data (statistics). CM, DD, AL, KVC, SW and FA designed tables and figures. The first draft of the article was written by CM, DD, SW, KVC and FA and all other authors revised the article for the final draft. All authors agreed with the final draft for publication.

Declaration of interest

The authors declare no competing interests.

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Ethics Committee approval

The study design was approved by the ethical commission of the University Hospitals of Leuven, who is the sponsor of the study (S25470 (ML9662); protocol version 4.3, 15-06-2018; Belgian registration number 322201420048). Ethical approval was obtained from the participating centres when indicated. The Erasmus

430 medical Centre of Rotterdam is the responsible ethics committee of the Netherlands (MEC-2013-10, protocol
431 version 4.3, 07-11-2018; NL4546.078.13, v09).

References

- 1 Eurostat. Mean age of women at childbirth and at birth of first child. Last acces on 01-03-2019.
- 2 Parazzini F, Franchi M, Tavani A, Negri E, Peccatori FA. Frequency of Pregnancy Related Cancer: A Population Based Linkage Study in Lombardy, Italy. *Int J Gynecol Cancer* 2017; **27**:613-9.
- 3 Smith LH, Danielsen B, Allen ME, Cress R. Cancer associated with obstetric delivery: results of linkage with the California cancer registry. *Am J Obstet Gynecol* 2003; **189**:1128-35.
- 4 El-Messidi A, Patenaude V, Hakeem G, Abenhaim HA. Incidence and outcomes of women with Hodgkin's lymphoma in pregnancy: a population-based study on 7.9 million births. *J Perinat Med* 2015; **43**:683-8.
- 5 Hoppe RT, Advani RH, Ai WZ, et al. NCCN Guidelines Insights: Hodgkin Lymphoma, Version 1.2018. *J Natl Compr Canc Netw* 2018; **16**:245-54.
- 6 Eichenauer DA, Aleman BMP, Andre M, et al. Hodgkin lymphoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2018; **29**:iv19-iv29.
- 7 Dauer LT, Thornton RH, Miller DL, et al. Radiation management for interventions using fluoroscopic or computed tomographic guidance during pregnancy: a joint guideline of the Society of Interventional Radiology and the Cardiovascular and Interventional Radiological Society of Europe with Endorsement by the Canadian Interventional Radiology Association. *J Vasc Interv Radiol* 2012; **23**:19-32.
- 8 Langagergaard V, Horvath-Puho E, Norgaard M, Norgard B, Sorensen HT. Hodgkin's disease and birth outcome: a Danish nationwide cohort study. *Br J Cancer* 2008; **98**:183-8.
- 9 Brenner B, Avivi I, Lishner M. Haematological cancers in pregnancy. *Lancet* 2012; **379**:580-7.
- 10 Aviles A, Nambo MJ, Neri N. Treatment of Early Stages Hodgkin Lymphoma During Pregnancy. *Mediterr J Hematol Infect Dis* 2018; **10**:e2018006.
- 11 de Haan J, Verheecke M, Van Calsteren K, et al. Oncological management and obstetric and neonatal outcomes for women diagnosed with cancer during pregnancy: a 20-year international cohort study of 1170 patients. *Lancet Oncol* 2018.
- 12 van Hasselt JG, van Calsteren K, Heyns L, et al. Optimizing anticancer drug treatment in pregnant cancer patients: pharmacokinetic analysis of gestation-induced changes for doxorubicin, epirubicin, docetaxel and paclitaxel. *Ann Oncol* 2014; **25**:2059-65.
- 13 Evens AM, Advani R, Press OW, et al. Lymphoma occurring during pregnancy: antenatal therapy, complications, and maternal survival in a multicenter analysis. *J Clin Oncol* 2013; **31**:4132-9.
- 14 Pinnix CC, Osborne EM, Chihara D, et al. Maternal and Fetal Outcomes After Therapy for Hodgkin or Non-Hodgkin Lymphoma Diagnosed During Pregnancy. *JAMA Oncol* 2016; **2**:1065-9.
- 15 Lishner M, Zemlickis D, Degendorfer P, Panzarella T, Sutcliffe SB, Koren G. Maternal and foetal outcome following Hodgkin's disease in pregnancy. *Br J Cancer* 1992; **65**:114-7.
- 16 Carbone PP, Kaplan HS, Musshoff K, Smithers DW, Tubiana M. Report of the Committee on Hodgkin's Disease Staging Classification. *Cancer Res* 1971; **31**:1860-1.
- 17 Eichenauer DA, Engert A, Andre M, et al. Hodgkin's lymphoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2014; **25 Suppl 3**:iii70-5.
- 18 Hasenclever D, Diehl V. A prognostic score for advanced Hodgkin's disease. International Prognostic Factors Project on Advanced Hodgkin's Disease. *N Engl J Med* 1998; **339**:1506-14.
- 19 Eurocat. Malformation Coding Guides. <http://www.eurocat-network.eu>. access on 01-08-2018.
- 20 Lishner M, Avivi I, Apperley JF, et al. Hematologic Malignancies in Pregnancy: Management Guidelines From an International Consensus Meeting. *J Clin Oncol* 2016; **34**:501-8.
- 21 Loibl S, Han SN, von Minckwitz G, et al. Treatment of breast cancer during pregnancy: an observational study. *Lancet Oncol* 2012; **13**:887-96.
- 22 Boerma T, Ronsmans C, Melesse DY, et al. Global epidemiology of use of and disparities in caesarean sections. *Lancet* 2018; **392**:1341-8.
- 23 World Health Organization DoRHaR. WHO recommendations for induction of labour. 2011.
- 24 Van Calsteren K, Heyns L, De Smet F, et al. Cancer during pregnancy: an analysis of 215 patients emphasizing the obstetrical and the neonatal outcomes. *J Clin Oncol* 2010; **28**:683-9.
- 25 Drew JH, Parkinson P, Walstab JE, Beischer NA. Incidences and types of malformations in newborn infants. *Med J Aust* 1977; **1**:945-9.
- 26 Merks JH, van Karnebeek CD, Caron HN, Hennekam RC. Phenotypic abnormalities: terminology and classification. *Am J Med Genet A* 2003; **123A**:211-30.
- 27 Klimm B, Goergen H, Fuchs M, et al. Impact of risk factors on outcomes in early-stage Hodgkin's lymphoma: an analysis of international staging definitions. *Ann Oncol* 2013; **24**:3070-6.
- 28 Moccia AA, Donaldson J, Chhanabhai M, et al. International Prognostic Score in advanced-stage Hodgkin's lymphoma: altered utility in the modern era. *J Clin Oncol* 2012; **30**:3383-8.
- 29 Eyre TA, Lau IJ, Mackillop L, Collins GP. Management and controversies of classical Hodgkin lymphoma in pregnancy. *Br J Haematol* 2015; **169**:613-30.

492 30 Amant F, Vandenbroucke T, Verheecke M, et al. Pediatric Outcome after Maternal Cancer Diagnosed
493 during Pregnancy. *N Engl J Med* 2015; **373**:1824-34.
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