bjh research paper

Maternal and neonatal outcomes in 80 patients diagnosed with non-Hodgkin lymphoma during pregnancy: results from the International Network of Cancer, Infertility and Pregnancy

Charlotte Maggen,[1] Daan Dierickx,[1,2] Elyce Cardonick,[3] Mina Mhallem Gziri,[4] Alvaro Cabrera-Garcia,[5] Roman G. Shmakov,[6] Irit Avivi,[7,8] Bianca Masturzo,[9] Johannes J. Duvekot,[10] Petronella B. Ottevanger,[11] Andie O'Laughlin,[12] Evgeniya Polushkina,[6] Kristel Van Calsteren,[13,14] F.J. Sherida H. Woei-A-Jin,[1,15] Frédéric Amant[1,16,17] and for the International Network on Cancer Infertility Pregnancy (INCIP)

[1]Department of Oncology, KU Leuven, Leuven, Belgium, [2]Department of Haematology, University Hospitals Leuven, Leuven, Belgium, [3]Department of Obstetrics and Gynaecology, Cooper, University Health Care, Camden, NJ, USA, [4]Department of Obstetrics, Cliniques Universitaires St Luc, UCL, Sint-Lambrechts-Woluwe, Belgium, [5]Hospital Regional de Alta Especialidad de Ixtapaluca (HRAEI) "Reference clinic for haemato-oncological diseases during pregnancy CREHER", Estado de México, México, [6]National Medical Research Centre for Obstetrics, Gynaecology and Perinatology named after Academician V.I. Kulakov of the Ministry of Healthcare of Russian Federation, Moscow, Russia, [7]Tel Aviv Sourasky Medical Centre,Tel Aviv, Israel, [8]Sackler Faculty of Medicine, TA University, Tel Aviv, Israel, [9]Department Surgical Sciences, University of Torino, Torino, Italy, [10]Department of Obstetrics and Gynaecology, Erasmus MC Cancer Institute, Rotterdam, The Netherlands, [11]Department of Medical Oncology, Radboud University Nijmegen Medical Centre, Nijmegen, Netherlands,

Summary

This cohort study of the International Network on Cancer, Infertility and Pregnancy (INCIP) reports the maternal and neonatal outcomes of 80 pregnant patients diagnosed with non-Hodgkin lymphoma (NHL) between 1986 and 2019, focussing on 57 (71%) patients with diffuse large B-cell lymphoma (DLBCL). Of all 80 patients, 54 (68%) pregnant patients received chemotherapy; mostly (89%) CHOP-like (cyclophosphamide, doxorubicin, vincristine, and prednisone) regimens. Four early pregnancies were terminated. Among 76 ongoing pregnancies, there was one stillbirth (1·3%). Overall, there was a high incidence of small for gestational age neonates (39%), preterm delivery (52%), obstetric (41%) and neonatal complications (12·5%), and this could not exclusively be explained by the receipt of antenatal chemotherapy. Half of preterm deliveries (46%) were planned in order to tailor oncological treatment. The 3-year progression-free and overall survival for patients with DLBCL treated with rituximab-CHOP was 83·4% and 95·7% for limited stage (n = 29) and 60·6% and 73·3% for advanced stage (n = 15). Of 36 pregnant patients who received rituximab, five (13%) cases with neonatal complications and three (8%) with maternal infections were reported. In conclusion, standard treatment for DLBCL can be offered to pregnant patients in obstetric centres that cater for high-risk patients.

Keywords: non-Hodgkin lymphoma, pregnancy, maternal outcome, diffuse large B-cell lymphoma, R-CHOP.

First published online 18 September 2020
doi: 10.1111/bjh.17103

© 2020 British Society for Haematology and John Wiley & Sons Ltd

[12]Cooper Medical School, Rowan University, Camden, NJ, USA, [13]Department of Obstetrics and Gynaecology, University Hospitals Leuven, Leuven, Belgium, [14]Department of Development and regeneration, KU Leuven, Leuven, Belgium, [15]Department of General Medical Oncology, University Hospitals Leuven, Leuven Cancer Institute, KU Leuven, Leuven, Belgium, [16]Department of Gynaecological Oncology, Amsterdam University Medical Centres, Amsterdam, The Netherlands, and [17]Department of Gynaecology, Antoni van Leeuwenhoek – Netherlands Cancer Institute, Amsterdam, The Netherlands

Received 22 June 2020; revised 14 August 2020; accepted for publication 19 August 2020
Correspondence: Frédéric Amant, MD, PhD, Centre of Gynaecologic Oncology Amsterdam, Antoni Van Leeuwenhoek, Netherlands Cancer Institute, Plesmanlaan 121, 1066 CX Amsterdam, The Netherlands.
E-mail: f.amant@nki.nl

Introduction

With worldwide, >509 000 reported cases in 2018, non-Hodgkin lymphoma (NHL) accounts for ~6% of all new cancer cases per year.[1] Diffuse large B-cell lymphoma (DLBCL) is the most common NHL subtype, diagnosed in 30–50% of cases. Mature T-cell and natural killer (NK) cell neoplasms are uncommon and the incidence varies greatly per geographic region and ethnic group.

In accordance with the age distribution, NHL is diagnosed less frequently in pregnancy than HL (respectively 5·39 vs. 8·06 per 100 000 births).[2,3] A recent large population-based study reported a rising prevalence, from 4·44 to 7·17 per 100 000 births over a 9-year period, which can be explained by the trend of delaying first childbirth and the age-dependent increased incidence of NHL.[2,4]

Management depends on the NHL subtype and stage. For most B-cell lymphomas, CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) with rituximab (R-CHOP), a monoclonal anti-CD20 antibody, with or without radiotherapy, is the standard of care.[5] Gestational age at diagnosis and the urgency of treatment determine the management in pregnant patients. Some consensus exists to defer treatment until after delivery in well selected cases of indolent NHL [e.g. follicular lymphoma (FL) Grade 1–3A].[6,7] Based on a literature study of 121 patients pregnancy-associated NHL is characterised by advanced stages, which may require immediate treatment.[8] Decision-making in pregnant patients is extremely challenging, especially in early pregnancy. To date, steroids or vinblastine, although not recommended as single agents for NHL, are suggested as a 'bridging treatment' until the second trimester of pregnancy, where chemotherapy can be initiated more safely.[7] Compared to breast cancer, literature on the antenatal treatment for NHL is scarce.[9–11] However, the CHOP regimen (cyclophosphamide 750 mg/m^2, doxorubicin 50 mg/m^2, vincristine 1·4 mg/m^2, prednisone 100 mg) shows considerable overlap with the commonly used AC regimen (cyclophosphamide 600 mg/m^2, doxorubicin 60 mg/m^2).[12] Although corticosteroids are given at higher equivalent dose in CHOP compared to AC, in which corticosteroids are given as anti-emetics, antenatal CHOP may be equally safe. Experience with antenatal rituximab in the context of NHL is based on a series of 24 pregnancies with reassuring neonatal outcomes.[6,13]

By assessing all NHL cases registered by the International Network on Cancer, Infertility and Pregnancy (INCIP), we aimed to gain more insight into: (i) the obstetric and neonatal outcome of CHOP-like regimens, with or without rituximab, during pregnancy; and (ii) maternal outcome of NHL. We selected all patients with DLBCL for an in-depth analysis. For survival analysis, we focussed on patients treated with standard R-CHOP.

Patients and methods

In 2005 an international registry for all cancers diagnosed in association with pregnancy was launched by the INCIP,

© 2020 British Society for Haematology and John Wiley & Sons Ltd

supported by the European Society of Gynaecological Oncology (ESGO). The database consists of oncological and obstetric data, voluntarily registered by members of the INCIP. This study was approved by the Ethics Committee of the University Hospital Leuven (Belgian number B322201421061) and approval was obtained from the participating centres when indicated.

Data from all patients diagnosed with NHL during pregnancy were retrieved from the INCIP registry in June 2019. Clinical data regarding disease characteristics, diagnosis, treatment, obstetric complications, neonatal outcome and maternal outcome were collected. All patients were staged according to the Ann Arbor classification and treated according to the local standards. The criteria of the International Prognostic Index for aggressive NHL (DLBCL, anaplastic large cell lymphoma, peripheral T-cell lymphoma and extranodal NK T-cell lymphoma) were not reported because of missing values.[14]

Patients who exclusively received antenatal radiotherapy were reported separately, as this approach is no longer recommended. According to current guidelines radiotherapy (when indicated) is initiated after induction polychemotherapy and preferentially is initiated postpartum to avoid fetal harm.[5,6] The neonatal and obstetric outcome of chemotherapy-exposed neonates was compared with non-exposed neonates. Outcomes of patients with DLBCL, the largest NHL subgroup, were reported separately. Small for gestational age (SGA) was defined as a birthweight <10th customised percentile corrected for gestational age, sex, maternal height, maternal weight, ethnicity and parity.[15]

The patients with DLBCL with ongoing pregnancies and available follow-up data were included for survival analysis. There were no patients with primary refractory disease. For patients with DLBCL treated with standard R-CHOP-like treatment [R-CHOP or R-EPOCH (rituximab, etoposide, prednisolone, vincristine, cyclophosphamide, and doxorubicin)] the maternal outcome was reported according to the stage at diagnosis (limited Stage I–II vs. advanced Stage III–IV) and the receipt of CHOP and rituximab during pregnancy. Progression-free survival (PFS) was defined as the interval between diagnosis and relapse or death. Overall survival (OS) was defined as the interval between diagnosis and death from any cause.

Data were collected in a Microsoft SQL Server Database. We used Fisher's exact test to compare groups on binary variables and the Mann–Whitney *U*-test for continuous variables. The Kaplan–Meier method was used to assess PFS and OS. Univariate analyses were performed by using Cox proportional hazards models. Statistical analysis was performed with the IBM Statistical Package for the Social Sciences (SPSS®), version 24 (IBM Corp., Armonk, NY, USA). Two-sided P values of ≤ 0.05 were considered statistically significant.

Results

Clinical characteristics

A total of 80 patients with a NHL diagnosis during pregnancy between 1986 and 2019 were identified (Table I, Fig 1). The median (range) age at diagnosis was 32 (16–41) years. Most patients (67·5%) were diagnosed during the second trimester of pregnancy. The most common subtype was DLBCL (57 of 80, 71%), followed by FL (six of 80, 8%). Extranodal disease was common (42%). Nine (26%) patients, eight with DLBCL and one with Burkitt lymphoma (BL), had reproductive organ involvement: breast ($n = 7$), uterus ($n = 1$) and vulva ($n = 1$).

Management

Three patients with aggressive NHL (one DLBCL, one unclassifiable with features intermediate between DLBCL and BL, and one anaplastic large-cell lymphoma) and one with FL, all diagnosed in the first trimester, opted for pregnancy termination. Two patients with advanced stage aggressive NHL and one with advanced stage BL, initiated (head or neck) radiotherapy in the second trimester of pregnancy (Table SI). Three other patients with BL were treated with chemotherapy, of whom one patient initiated treatment after a planned preterm delivery. All patients with indolent NHL (six with FL and one with hairy cell leukaemia) started with treatment after pregnancy termination ($n = 1$) or delivery at a median (range) of 12 (2–32) weeks.

In total, 54 (68%) patients with NHL were treated with chemotherapy from the second trimester of pregnancy onwards (Table SII). For 46 pregnant patients with DLBCL treated with chemotherapy, CHOP, with or without rituximab, was the most common regimen (80%). The other 11 patients with DLBCL (20%) had a deferral of treatment until after pregnancy termination ($n = 1$) or delivery ($n = 10$). Over the years, more patients initiated chemotherapy during pregnancy ($P = 0{\cdot}040$) and there were more SGA neonates ($P = 0{\cdot}099$) (Fig 2). The proportion of preterm deliveries decreased over time ($P = 0{\cdot}343$) and the number of obstetric and neonatal complications remained relatively stable over time.

Obstetric outcome

In all, 75 ongoing pregnancies (all NHL subtypes) culminated in a live birth. There were 28 (37%) spontaneous deliveries, two (3%) preterm emergency caesarean sections and 45 (60%) planned deliveries (Table SIII). Of 39 preterm deliveries, 14 (36%) patients delivered spontaneously, seven (18%) delivered as emergencies for medical or obstetric reasons and 18 (46%) had a planned delivery for therapy planning. One pregnancy ended in a stillbirth after extensive vaginal bleeding, suggestive of placental abruption, prior to initiation of cancer treatment.

© 2020 British Society for Haematology and John Wiley & Sons Ltd

Table I. Clinical characteristics of patients diagnosed with non-Hodgkin lymphoma during pregnancy.

Characteristic	Non-Hodgkin lymphoma (n = 80)	Diffuse large B-cell lymphoma (n = 57)
Age at diagnosis, years, median (range, IQR)	32 (16–41, 7)	32·0 (16–40, 7·5)
<21 years, n (%)	8 (10·0)	5 (8·8)
21–25 years, n (%)	5 (6·3)	4 (7·0)
26–30 years, n (%)	22 (27·5)	15 (26·3)
31–35 years, n (%)	30 (37·5)	22 (38·6)
>35 years, n (%)	15 (18·8)	11 (19·3)
Gestational age at diagnosis, weeks, median (range, IQR)	22 (1–38, 10)	22 (1–38, 9)
First trimester, n (%)	9 (11·3)	5 (8·8)
Second trimester, n (%)	54 (67·5)	40 (70·2)
Third trimester, n (%)	17 (21·3)	12 (21·1)
Non-Hodgkin lymphoma (WHO, 2008), n (%)		
Follicular lymphoma	6 (7·5)	
Diffuse large B-cell lymphoma	57 (71·3) *12 (15.0)*	57 (100) *12 (21.1)*
Primary mediastinal B-cell lymphoma		
Hairy cell leukaemia	1 (1·3)	
Burkitt lymphoma	4 (5·0)	
Anaplastic large-cell lymphoma	5 (6·3)	
Extranodal NK T-cell lymphoma	1 (1·3)	
Peripheral T-cell lymphoma	2 (2·5)	
Unclassifiable, with features between	1 (1·3)	
DLBCL and Burkitt lymphoma	–	
Not reported	3 (3·8)	
Prior pregnancies, n (%)		
Nulliparous	40 (50·0)	29 (50·9)
Multiparous	39 (48·8)	27 (47·4)
Not reported	1 (1·3)	1 (1·8)
Ann Arbor Stage, n (%)		
I	19 (23·8)	15 (26·3)
II	21 (26·3)	19 (33·3)
III	9 (11·3)	4 (7·0)
IV	24 (30·0)	15 (26·3)
Not reported	7 (8·8)	4 (7·0)
B-symptoms, n (%)		
Yes	47 (58·8)	22 (38·6)
No	28 (35·0)	31 (54·4)
Not reported	5 (6·3)	4 (7·0)
Bulky disease, n (%)		
Yes	12 (15·0)	11 (19·3)
No	67 (83·8)	45 (78·9)
Not reported	1 (1·3)	1 (1·8)
Extranodal disease, n (%)		
Yes	34 (42·5)	22 (38·6)
More than one sides affected	10 (29·4)	7 (12·3)
Reproductive organs affected	9 (26·5)	8 (14·0)
No	45 (56·3)	34 (59·6)
Not reported	1 (1·3)	1 (1·8)
Treatment during pregnancy, n (%)		
No treatment during pregnancy	23 (28·8)	11 (19·3)
Pregnancy termination	4 (17·4)	1 (9·1)
Stillbirth	1 (4·3)	0 (0)
CHOP-like after delivery	9 (39·1)	7 (63·6)
Other chemotherapy after delivery	9 (39·1)	3 (27·3)
Chemotherapy, n (%)	54 (67·5)	46 (80·7)
CHOP	10 (18·5)	7 (15·2)
R-CHOP	33 (61·1)	30 (65·2)
EPOCH[$]	3 (5·6)	2 (4·3)
R-EPOCH	2 (3·7)	2 (4·3)
Other**	6 (11·1)	5 (10·9)
Radiotherapy, n (%)	3 (3·8)	0 (0)
Rituximab during pregnancy, n (%)	36 (45·0)	33 (57·9)
Pregnancy outcome, n (%)		
Live birth	75 (93·8)	56 (98·2)
Stillbirth	1 (5)	0 (0)
Termination of pregnancy	4 (1·3)	1 (1·8)
Preterm delivery*, n (%)	39 (52·0)	29 (51·8)
Follow-up of patients, months, mean (range, IQR)	51·5 (1–358, 58)	37·8 (1–184, 48)
Complete remission, n (%)	55 (68·8)	42 (73·7)
Recurrent disease, n (%)	9 (11·3)	6 (10·5)
Deceased, n (%)	9 (11·3)	5 (8·8)
Lost in follow-up after delivery, n (%)	7 (8·8)	4 (7·0)

IQR, interquartile range; NHL, non-Hodgkin lymphoma; NK, natural killer; WHO, World Health Organization.
(R-)CHOP, (rituximab-) cyclophosphamide, doxorubicin, vincristine.
(R-)EPOCH, (rituximab-) etoposide, vincristine, cyclophosphamide, doxorubicin.
MACOP-B, methotrexate (not given during pregnancy), doxorubicin, cyclophosphamide, vincristine, bleomycin.
VACOP-B, etoposide, doxorubicin, cyclophosphamide, vincristine, bleomycin.
R-ACVPB, rituximab, doxorubicin, cyclophosphamide, vindesine, bleomycin.
*Only including live births.
**Doxorubicin monotherapy, MACOP-B, VACOP-B, R-ACVPB.
[$]including one dose-adjusted approach EPOCH.

© 2020 British Society for Haematology and John Wiley & Sons Ltd

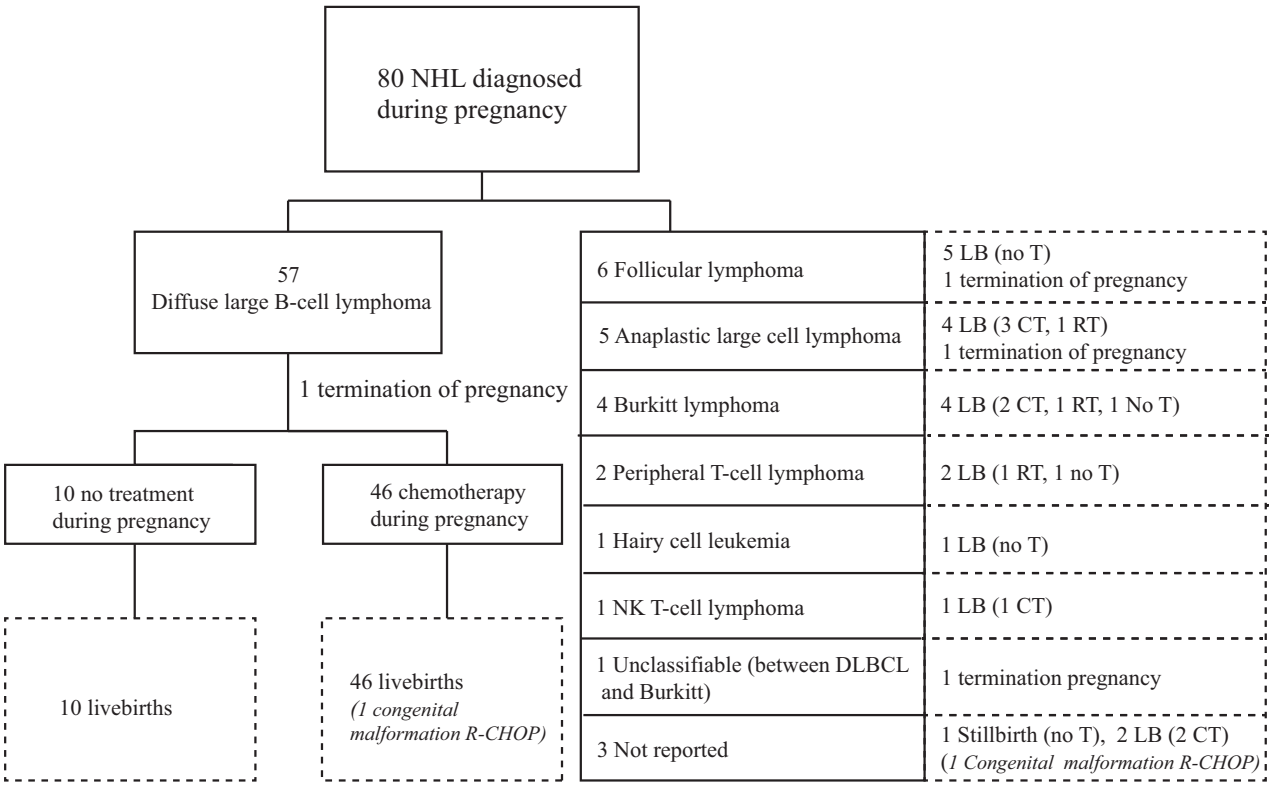


Fig 1. Flowchart of patients included in the cohort study. NHL, non-Hodgkin lymphoma; DLBCL, diffuse large B-cell lymphoma; NK, natural killer; CT, chemotherapy during pregnancy; RT, radiotherapy during pregnancy; no T, no treatment during pregnancy; LB, livebirth; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine.

More than half of the patients diagnosed with DLBCL (29 of 56, 52%) delivered preterm. Compared to patients who were not treated during pregnancy, the receipt of antenatal chemotherapy was not associated with increased rates of preterm delivery ($P = 1{\cdot}000$, Table SIV). Thirteen pregnant patients (23%) who initiated chemotherapy had spontaneous preterm labour (range 29–36 weeks). Most patients (32 of 56, 57%) delivered vaginally. Preterm rupture of membranes, preterm contractions and maternal infection were the most frequent reported obstetric complications (Table SIV).

Neonatal outcome

Two children prenatally exposed to R-CHOP after the first trimester of pregnancy, were born with an anomaly (a ventricular septal defect and duplex right kidney), resulting in a congenital malformation rate of 2·9% (two of 70 neonates with known outcome) (Table SV).

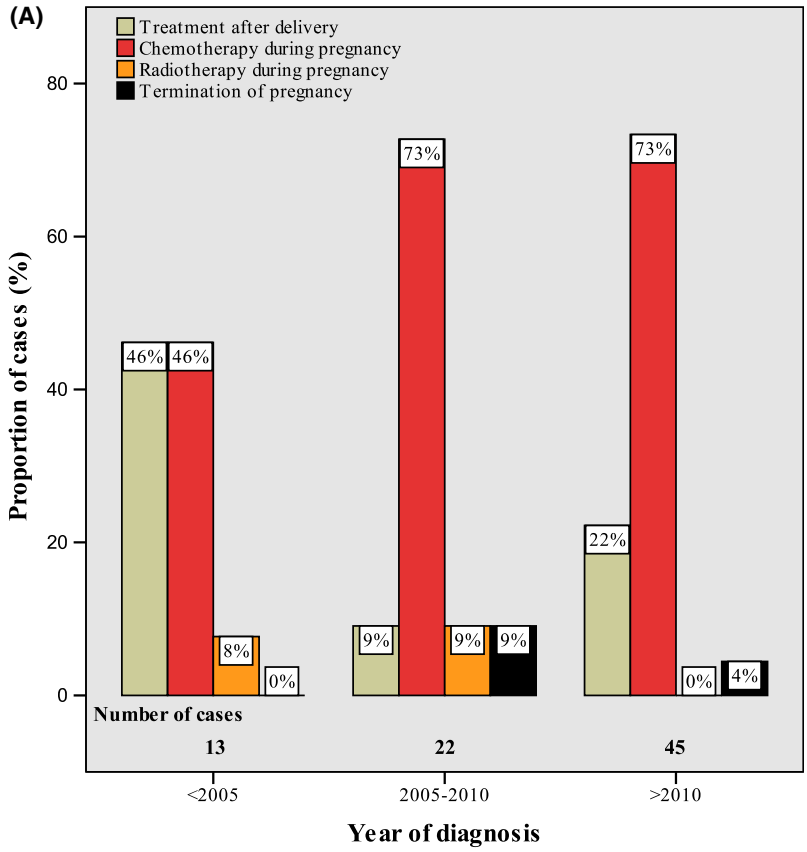
In total, 24 of 56 neonates (44·4%) of patients diagnosed with DLBCL were SGA (Table II). Birth weight percentiles in 46 children prenatally exposed to cancer treatment did not differ statistically from 10 non-exposed children ($P = 0{\cdot}672$). The results are similar for the entire cohort (54 chemotherapy-exposed vs. 18 non-exposed; $P = 0{\cdot}215$). Further subanalysis did not reveal a difference in birthweight percentiles according to DLBCL stage or the receipt of antenatal rituximab ($P = 0{\cdot}077$ and $P = 0{\cdot}673$ respectively). Major neonatal complications and admissions to the Neonatal Intensive Care Unit (NICU) were comparable for chemotherapy-exposed and non-exposed neonates (Table SVI). Prematurity was the main reason for NICU admission (15 of 17, 88%).

One infant, prenatally exposed to R-CHOP and born at 32 weeks of gestation, died at 9 days of life due to sepsis. Five of 36 neonates prenatally exposed to rituximab were admitted to the NICU with mainly prematurity-related complications (including three cases with neonatal systemic infections and one with neonatal neutropenia, 3 weeks after the last R-CHOP administration). Two of five neonates prenatally exposed to etoposide-based chemotherapy, delivered at 35 and 37 weeks of gestation and had respiratory difficulties requiring NICU admission.

Maternal outcome

With a median (range) follow-up of 38 (1–184) months, 52 pregnant patients with DLBCL had a 3-year PFS and OS of 77·5% and 90·0% respectively (Fig 3). Pregnant patients with limited stage DLBCL treated with R-CHOP ($n = 29$) had a 3-year PFS and OS of 83·4% and 95·7% respectively (Fig 4A). For advanced stage ($n = 15$), the 3-year PFS and

© 2020 British Society for Haematology and John Wiley & Sons Ltd



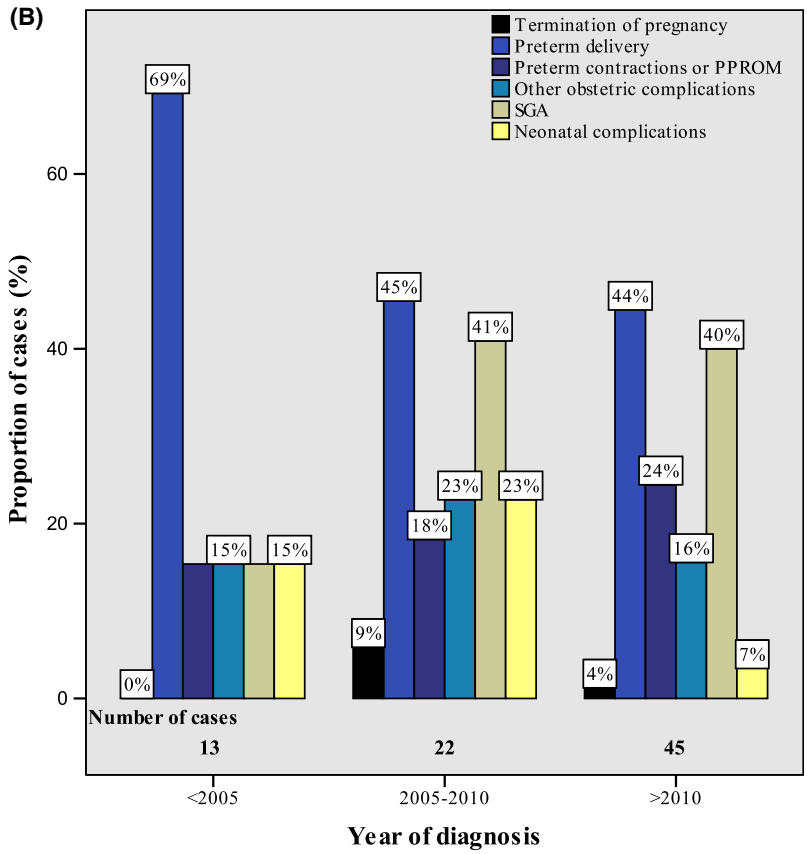


Fig 2. (A) Evolution of management during pregnancy and (B) obstetric and neonatal outcome of NHL during pregnancy (n = 80), from 1986 to 2019. Other obstetric complications includes: stillbirth, hypertensive disorder, gestational diabetes, maternal infection requiring antibiotics, antepartum bleeding, and thrombosis. Neonatal complications includes: neonatal death, idiopathic respiratory distress syndrome, neonatal sepsis, neutropenia, reversible reduced ejection fraction and neutropenia For the three categories (<2005, 2005–2010 and >2010) the distribution of Stage I–II NHL was 69%, 41%, 49%; Stage III NHL was 0%, 0%, 20%; of Stage IV NHL 31%, 50%, 20%; for follicular lymphoma 15%, 5%, 7%; for Burkitt lymphoma 15%, 5%, 2%, respectively. PPROM, preterm premature rupture of the membranes; SGA, small for gestational age. [Colour figure can be viewed at wileyonlinelibrary.com]

© 2020 British Society for Haematology and John Wiley & Sons Ltd

Table II. Neonatal outcome of children born from patients with NHL*.

Neonatal outcome	All (n = 72) N (%)	DLBCL All (n = 56) N (%)	Chemotherapy (n = 46) N (%)	No antenatal treatment (n = 10) n/N (%)	P
Gestational Age at delivery					0·692
$37^{0/7}$–41	35 (48·6)	27 (48·2)	22 (47·8)	5/10 (50·0)	
$34^{0/7}$–$36^{6/7}$	21 (29·2)	19 (33·9)	17 (37·0)	2/10 (20·0)	
$32^{0/7}$–$33^{6/7}$	12 (16·7)	6 (10·7)	4 (8·7)	2/10 (20·0)	
$28^{0/7}$–$31^{6/7}$	4 (5·6)	4 (7·1)	3 (6·5)	1/10 (10·0)	
Birthweight, g					0·789
<2000	9 (13·0)	7 (13·0)	5 (11·4)	2/10 (20·0)	
2000–2499	23 (33·3)	19 (35·2)	15 (34·1)	4/10 (40·0)	
2500–2999	25 (36·2)	21 (38·9)	18 (40·9)	3/10 (30·0)	
>3000	12 (17·4)	7 (13·0)	6 (13·6)	1/10 (10·0)	
Missing	3 (2.78)	2 (3.57)	2 (4.35)	0/10 (10.0)	
Birthweight percentile					0·672
<P10	28 (38·9)	24 (44·4)	20 (45·5)	4/10 (40·0)	
P10–P24	9 (12·5)	6 (11·1)	4 (9·1)	2/10 (20·0)	
P25–P49	14 (19·4)	13 (24·1)	12 (27·3)	1/10 (10·0)	
P50–P74	12 (16·7)	7 (13·0)	5 (11·4)	2/10 (20·0)	
P75–P90	1 (1·4)	0 (0)	0 (0)	0/10 (0)	
>P90	5 (6·9)	4 (7·4)	3 (6·8)	1/10 (10·0)	
Missing	3 (2.78)	2 (3.57)	2 (4.35)	0/10 (0)	
Major congenital malformations					
Yes	2 (3·0)	1 (1·9)	1 (2·4)	0/10 (0)	
No	65 (97·0)	51 (98·1)	41 (97·6)	10/10 (100·0)	
Missing	5 (6·9)	4 (7·4)	4 (9·1)	0/10 (0)	1·000
Major neonatal complications**					1·000
Yes	9 (13·6)	7 (13·5)	6 (14·3)	1/10 (10·0)	
No	57 (86·4)	45 (86·5)	36 (85·7)	9/10 (90·0)	
Missing	6 (8.33)	4 (7·4)	4 (9·1)	0/10 (0)	
NICU admission					1·000
Yes	22 (33·8)	17 (33·3)	14 (34·1)	3/10 (30·0)	
No	42 (64·6)	34 (66·7)	27 (65·9)	7/10 (70·0)	
Missing	7 (9.72)	5 (8.93)	5 (11·4)	0/10 (0)	

NICU, Neonatal Intensive Care Unit; SGA, small for gestational age.

*Analysis of all live births, excluding three neonates prenatally exposed to radiotherapy.

**Including neonatal death, idiopathic respiratory distress syndrome, neonatal sepsis, neutropenia, reversible reduced ejection fraction and neutropenia.

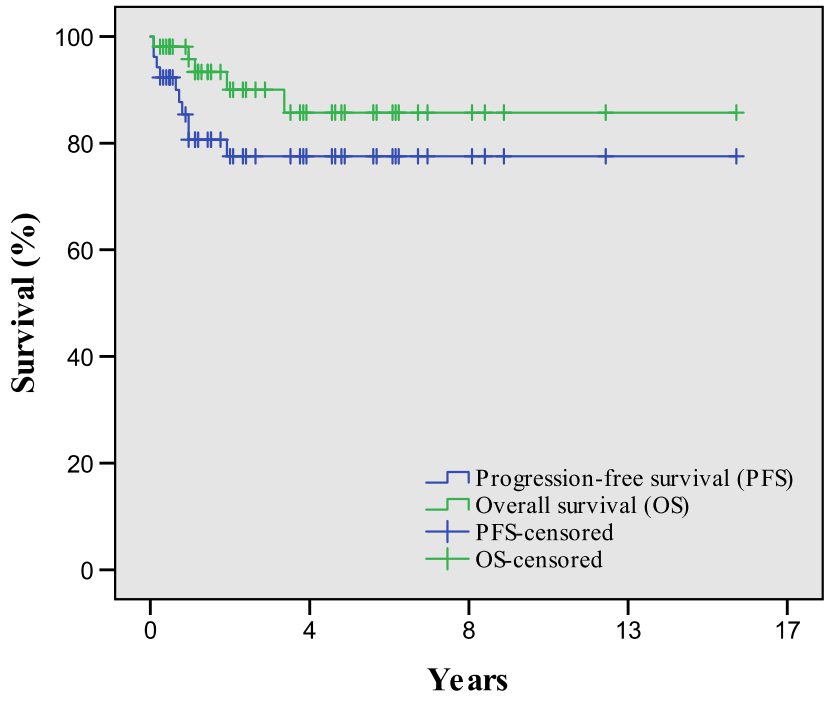
OS were 60·6% and 73·3% respectively (Fig 4B). The association of rituximab in 17 limited stage pregnant patients with DLBCL treated with CHOP resulted in an excellent survival (PFS 91·7% and OS 100·0%) compared to seven patients with limited stage DLBCL who received rituximab after pregnancy (PFS 62·5% and OS 87·5%) (P = 0·078). All pregnant patients with advanced stage disease treated with CHOP (n = 12) received rituximab.

Seven patients deferred treatment until after delivery. Four of them initiated treatment after delivery with a 1–3 week delay since diagnosis. The other three patients, including two patients with advanced stage disease, were diagnosed in the first half of pregnancy and declined antenatal chemotherapy. They received supportive treatment, including steroids, and delivered after 37 weeks. The median (range) treatment delay was 24 (20–26) weeks and the median (range) follow-up was 12 (6–14) months. None of these seven patients relapsed or died.

Discussion

In the present study, we report the maternal and neonatal outcome of 80 pregnant patients diagnosed with NHL between 1986 and 2019. Most patients initiated chemotherapy during pregnancy (68%), with a rising trend over time. As a result, observational data revealed more SGA and preterm contractions or preterm premature rupture of the membranes (PPROM) over time; however, less preterm births, explained by the tendency to aim for term deliveries to safeguard neonatal outcomes. Overall, the incidence of

© 2020 British Society for Haematology and John Wiley & Sons Ltd



Number at risk (cases censored)

OS	52 (0)	16 (31)	5 (11)	1 (4)	0 (0)
PFS	52 (0)	16 (26)	5 (11)	1 (4)	0 (0)

Fig 3. Progression-free survival (PFS) and overall survival (OS) of patients diagnosed with DLBCL during pregnancy (n = 52). Patients who terminated pregnancy before treatment initiation were excluded. The 3-year PFS and OS of the 52 pregnant patients with DLBCL is 77·5% and 90·0% respectively. [Colour figure can be viewed at wileyonlinelibrary.com]

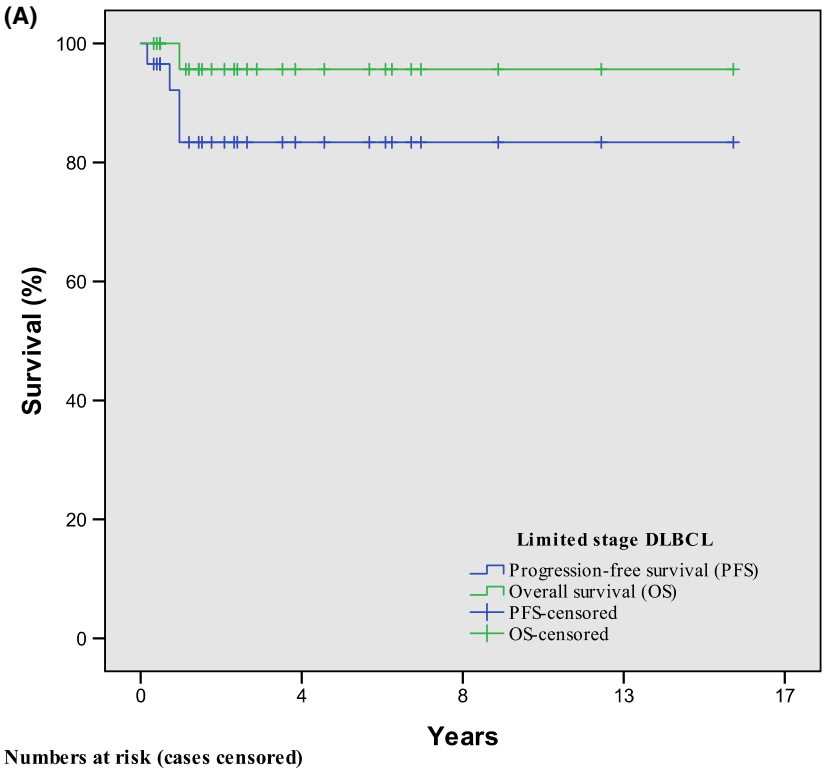
preterm delivery (52%), obstetric (41%) and neonatal (12·5%) complications and SGA neonates (39%) was high; however, this was not exclusively explained by the receipt of antenatal chemotherapy. Therapy planning was the main reason for preterm delivery. The 3-year PFS and OS for the 52 patients with DLBCL treated with R-CHOP was 77·5% and 90·0% respectively and is comparable to the expected survival in the non-pregnant population. In the present series, antenatal administration of rituximab during the second and third trimester of pregnancy (range 13–35 weeks) in combination with chemotherapy in 36 cases resulted in five (13%) neonatal complications and three (8%) maternal infections.

A literature search study identified 121 pregnant patients from 74 papers diagnosed with NHL between 1967 and 2011.[8] In total, 39 had BL and 39 had DLBCL (36%), at a predominantly advanced stage (85% vs. 62%). In contrast, Evens *et al.*[10] published a multicentre cohort study of 50 pregnant patients with NHL, including 28 patients with DLBCL, and 40% had advanced disease. Our present series reports on the largest DLBCL cohort to date (n = 57), of whom 41% had advanced stage disease. The previously reported high rate of extranodal involvement in the pregnant population was confirmed in our present series (42%), with affected reproductive organs in 26·5% of patients.[8] This latter phenomenon might be explained by the increased blood supply during gestation or the presence of gestational hormonal receptors on malignant lymphocytes.[8]

A large population-based study, including 427 patients with pregnancy-associated NHL, reported high maternal and fetal morbidity and mortality compared to 7 916 388 controls: that is, pre-eclampsia (6·3%), caesarean section (39·8%), preterm birth (17·1%), postpartum blood transfusions (15·7%) and maternal infections (1·17%).[2,3] However, that study did not included details on gestational age, stage at diagnosis or management. Also, histological NHL classification was not reported in 81·5% of cases. The present INCIP series confirmed a high incidence of complications, with a high rate of preterm delivery (52%). Evens *et al.*[10] and Pinnix *et al.*[11] (eight pregnant patients with NHL) also reported a preterm delivery rate of 50%, but failed to demonstrate an increased risk of adverse outcomes for patients with antenatal treatment compared to patients with deferred treatment. As preterm delivery is associated with neonatal comorbidities, including impaired neurocognitive function, planned preterm delivery is no longer advised, unless justified by maternal factors.[16] In patients with advanced cancer with systemic burden or in patients who need treatment that is not compatible with pregnancy, preterm delivery seems reasonable. In general, a delivery after 37 weeks should be aimed for, whenever maternal and fetal factors allow.

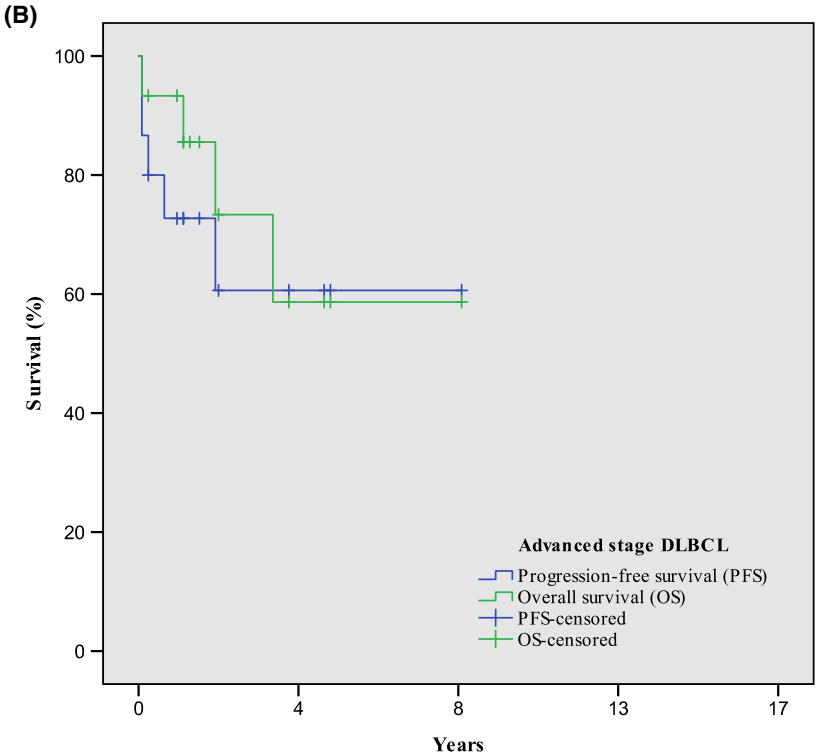
The reported caesarean section rate (41%) is similar to the published rates in the pregnant cancer population; however, is much higher than the worldwide incidence of 21·1%.[17]

© 2020 British Society for Haematology and John Wiley & Sons Ltd



Numbers at risk (cases censored)

OS	29 (0)	9 (19)	3 (6)	1 (2)	0 (0)
PFS	29 (0)	9 (16)	3 (6)	1 (2)	0 (0)



Numbers at risk (cases censored)

OS	15 (0)	3 (7)	1 (2)	0 (1)	0 (0)
PFS	15 (0)	3 (7)	1 (2)	0 (1)	0 (0)

Fig 4. Progression-free survival (PFS) and overall survival (OS) of limited and advanced stage NHL treated with R-CHOP-like regimens. The 3-year PFS and OS was for limited stage DLBCL (n = 29) was 83·4% and 95·7% (A) and for advanced stage DLBCL (n = 15) 60·6% and 73·3% (B). [Colour figure can be viewed at wileyonlinelibrary.com]

© 2020 British Society for Haematology and John Wiley & Sons Ltd

This is probably explained by the high rate of preterm delivery or the desire for a controlled delivery in oncological patients. However, in general a vaginal delivery should be preferred if possible, unless there are obstetric or medical contraindications.[18]

The hypercoagulable state in this population demands for consideration of prophylactic low-molecular-weight heparins (LMWHs).[6] In the present series, the use of prophylactic LMWHs was absent for the majority of cases; however, local policies of most participating centres currently recommend LMWHs in pregnant patients with lymphoma. One pregnant patient who developed thromboembolism did not receive prophylactic LMWHs.

The present cohort study revealed a congenital malformation rate of 2·8%, which is comparable to the expected rate in the general population (between 2.8 and 6.9% for major malformations).[19,20] As the malformations occurred in two neonates prenatally exposed to R-CHOP after the first trimester of pregnancy and had a different pattern, the causality of chemotherapy seems unlikely. It is well established that pregnant patients with cancer are at higher risk of delivering SGA neonates and this risk appears to be associated with the receipt of antenatal chemotherapy.[21,22] The recent INCIP data on HL revealed an incidence of SGA of 21% and chemotherapy-exposed neonates had lower percentiles compared to non-exposed neonates ($P = 0{\cdot}035$).[22] A large cohort on different cancer types confirmed a high chemotherapy-associated incidence of SGA.[21] The relatively low numbers in the present NHL series could not reveal an association between antenatal chemotherapy and SGA. However, similarly to antenatal chemotherapy, observational data revealed an increased incidence of SGA and preterm contractions or PPROM over time, both well-known adverse effects of antenatal chemotherapy. Also, the overall incidence of SGA was high (39%), potentially reflecting the systemic nature of NHL with a poor maternal general health and nutritional status. Corticosteroid use may also contribute to a lower birthweight. A large prospective study assessing intra-uterine fetal growth, maternal risk factors (including cancer stage) and cumulative chemotherapy dosages may provide a better insight into the multifactorial cause of SGA in the pregnant population with cancer.

Survival of NHL in the non-pregnant population depends on stage and NHL subtype. For young patients with low-risk DLBCL treated with R-CHOP event-free survival and OS is 79% and 93% respectively.[5] Survival of 52 pregnant patients with DLBCL in the present series was comparable, even though not all were treated with standard R-CHOP and some had a pregnancy-related treatment delay. Remarkably, no negative events were registered for seven patients with DLBCL who opted for treatment deferral until after delivery. However, these results should be interpreted with caution because of the low numbers and limited follow-up data for some of the included patients. Based on the non-pregnant population, DLBCL treatment should ideally not be delayed for >1 month in order not to impair survival.[23,24] As randomised controlled trials in pregnant women are ethically not possible, only observational studies are available. The available literature on rituximab during pregnancy, mainly based on case series of pregnant patients with autoimmune disease such as rheumatoid disease or multiple sclerosis, suggests reassuring obstetric and neonatal outcomes following second or third trimester exposure [6,13,25] However, rituximab should still be used with caution during pregnancy as the immunoglobulin receptor-mediated placental transfer increases with gestational age and potentially puts the fetus (and the mother) at risk of infections by B-cell depletion.[13] Furthermore, concomitant use of chemotherapy may increase the risk of infection. Unfortunately, available data are still too scarce to explore the effect of gestational age at exposure or repetitive administrations of rituximab. As rituximab is expected to improve DLBCL survival rates by 15–20%, its use can be considered as the benefits for the mother outweigh the (neonatal) risks.[5] Survival in pregnant patients who received rituximab in the present series was excellent and comparable to the expected survival rates in the non-pregnant population.[5]

An important limitation of the present study was it retrospective design. Apart from the low relapse rate in DLBCL, the low numbers included possibly explains why we could not identify risk factors for survival. In addition, no recommendations can be given with regard to the safety of etoposide for peripheral T-cell lymphoma and double-hit lymphomas, as numbers were too low. Also, the design of the INCIP registry did not allow histopathological review. However, NHL during pregnancy is extremely rare, and observational studies are the only way to investigate this population. Continuous international collaboration is encouraged and gives a better insight in the clinical aspects of the pregnant cancer population.

In conclusion, treatment of DLBCL with CHOP-like regimens during pregnancy can be considered after the first trimester of pregnancy, with reassuring maternal and neonatal outcomes. Addition of rituximab to CHOP for DLBCL can be considered. Follow-up of pregnant patients with NHL in an obstetric unit that caters for high-risk patients is recommended as preterm delivery, disease-related SGA neonates and prematurity-related neonatal complications are common.

Funding information

The European Union's Horizon 2020 research and innovation programme under grant agreement No 647047 and Kom Op Tegen Kanker (Stand up to Cancer), the Flemish Cancer Society funds the INCIP. Frédéric Amant is the senior clinical investigator of the Research Foundation Flanders (F.W.O) and the project receives support from the ESGO.

Acknowledgements

We thank all participating patients and all (para-)medical staff involved in registering cases in the INCIP database (see

© 2020 British Society for Haematology and John Wiley & Sons Ltd

www.cancerinpregnancy.org). We especially thank INCIP investigators Carolina Balderas Delgado (CREHER clinic, Mexico) and Ingrid A. Boere (Erasmus MC, the Netherlands) for collecting cases and their scientific support. We thank the ESGO for their continued support.

Author contributions

Frédéric Amant, Charlotte Maggen and Daan Dierickx designed the study. All authors were involved in data collection. Data analysis was performed by Frédéric Amant, Charlotte Maggen, Daan Dierickx and F.J. Sherida H. Woei-A-Jin. Charlotte Maggen performed statistical analyses and designed the tables and figures. The first draft of the manuscript was written by Frédéric Amant, Charlotte Maggen, Daan Dierickx and F.J. Sherida H. Woei-A-Jin and all authors reviewed and approved the final version.

Conflict of interests

The authors declare no competing interests.

Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table SI. Cases with radiotherapy during pregnancy for non-Hodgkin lymphoma (n = 3).

Table SII. Chemotherapy regimens and gestational age at NHL treatment initiation.

Table SIII. Obstetric outcome of ongoing pregnancies (n = 75)*.

Table SIV. Reported obstetric complications of patients with NHL**.

Table SV. Reported congenital malformations.

Table SVI. Reported stillbirth and neonatal complications (n = 9).

References

1. GLOBACAN 2018 data. Available from: http://gco.iarc.fr/. Accessed 13 November 2018.
2. El-Messidi A, Patenaude V, Abenhaim HA. Incidence and outcomes of women with non-Hodgkin's lymphoma in pregnancy: a population-based study on 7.9 million births. *J Obstet Gynaecol Res*. 2015;**41**:582–9.
3. 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.
4. Howlader NNA, Krapcho M, Miller D, Brest A, Yu M, Ruhl J, et al. (eds). SEER Cancer Statistics Review, 1975–2016, National Cancer Institute. Bethesda, MD, https://seer.cancer.gov/csr/1975_2016/, based on November 2018 SEER data submission, posted to the SEER web site, April 2019.
5. Pfreundschuh M, Kuhnt E, Trumper L, Osterborg A, Trneny M, Shepherd L, et al. CHOP-like chemotherapy with or without rituximab in young patients with good-prognosis diffuse large-B-cell lymphoma: 6-year results of an open-label randomised study of the MabThera International Trial (MInT) Group. *Lancet Oncol*. 2011;**12**:1013–22.
6. Lishner M, Avivi I, Apperley JF, Dierickx D, Evens AM, Fumagalli M, et al. Hematologic Malignancies in Pregnancy: Management Guidelines From an International Consensus Meeting. *J Clin Oncol*. 2016;**34**:501–8.
7. Odelia A, Erel J, Chava P, Yair H, Nadav S, Michael L, et al. Continuing dilemmas in the management of lymphoma during pregnancy: review of a 10-point case-based questionnaire. *Int J Clin Oncol*. 2017;**22**:190–9.
8. Horowitz NA, Benyamini N, Wohlfart K, Brenner B, Avivi I. Reproductive organ involvement in non-Hodgkin lymphoma during pregnancy: a systematic review. *Lancet Oncol*. 2013;**14**:e275–82.
9. Avivi I, Farbstein D, Brenner B, Horowitz NA. Non-Hodgkin lymphomas in pregnancy: tackling therapeutic quandaries. *Blood Rev*. 2014;**28**:213–20.
10. Evens AM, Advani R, Press OW, Lossos IS, Vose JM, Hernandez-Ilizaliturri FJ, et al. Lymphoma occurring during pregnancy: antenatal therapy, complications, and maternal survival in a multicenter analysis. *J Clin Oncol*. 2013;**31**:4132–9.
11. Pinnix CC, Osborne EM, Chihara D, Lai P, Zhou S, Ramirez MM, et al. Maternal and fetal outcomes after therapy for Hodgkin or non-Hodgkin lymphoma diagnosed during pregnancy. *JAMA Oncol*. 2016;**2**:1065–9.
12. Loibl S, Schmidt A, Gentilini O, Kaufman B, Kuhl C, Denkert C, et al. Breast cancer diagnosed during pregnancy: adapting recent advances in breast cancer care for pregnant patients. *JAMA Oncol*. 2015;**1**:1145–53.
13. Chakravarty EF, Murray ER, Kelman A, Farmer P. Pregnancy outcomes after maternal exposure to rituximab. *Blood*. 2011;**117**:1499–506.
14. International Non-Hodgkin's Lymphoma Prognostic Factors Project. A predictive model for aggressive non-Hodgkin's lymphoma. *N Engl J Med*. 1993;**329**:987–94.
15. Gardosi JF, Williams M, Hugh O, Ford C, Qasam M. Customised Centile Calculator GROW v8.0.4. Gestation Network wwwgestationnet. 2019.
16. Amant F, Vandenbroucke T, Verheecke M, Fumagalli M, Halaska MJ, Boere I, et al. Pediatric outcome after maternal cancer diagnosed during pregnancy. *N Engl J Med*. 2015;**373**:1824–34.
17. Boerma T, Ronsmans C, Melesse DY, Barros AJD, Barros FC, Juan L, et al. Global epidemiology of use of and disparities in caesarean sections. *Lancet*. 2018;**392**:1341–8.
18. Amant F, Berveiller P, Boere IA, Cardonick E, Fruscio R, Fumagalli M, et al. Gynecologic cancers in pregnancy: guidelines based on a third international consensus meeting. *Ann Oncol*. 2019;**30**:1601–12.
19. Drew JH, Parkinson P, Walstab JE, Beischer NA. Incidences and types of malformations in newborn infants. *Med J Aust*. 1977;**1**:945–9.
20. Merks JH, van Karnebeek CD, Caron HN, Hennekam RC. Phenotypic abnormalities: terminology and classification. *Am J Med Genet A*. 2003;**123A**:211–30.
21. de Haan J, Verheecke M, Van Calsteren K, Van Calster B, Shmakov RG, Mhallem Gziri M, 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;**19**:337–46
22. Maggen C, Dierickx D, Lugtenburg P, Laenen A, Cardonick E, Smakov R, et al. Obstetric and maternal outcomes in patients diagnosed with Hodgkin lymphoma during pregnancy: a multicentre, retrospective, cohort study. *Lancet Haematol*. 2019;**6**:e551–61.
23. Olszewski AJ, Ollila T, Reagan JL. Time to treatment is an independent prognostic factor in aggressive non-Hodgkin lymphomas. *Br J Haematol*. 2018;**181**:495–504.
24. Phipps C, Lee YS, Ying H, Nagarajan C, Grigoropoulos N, Chen Y, et al. The impact of time from diagnosis to treatment in diffuse large B-cell lymphoma. *Leuk Lymphoma*. 2018;**59**:2336–41.
25. Das G, Damotte V, Gelfand JM, Bevan C, Cree BAC, Do L, et al. Rituximab before and during pregnancy: a systematic review, and a case series in MS and NMOSD. *Neurol Neuroimmunol Neuroinflamm*. 2018;**5**:e453.

© 2020 British Society for Haematology and John Wiley & Sons Ltd