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PROGNOSTIC FACTORS FOR OBSTETRIC AND ONCOLOGICAL OUTCOME IN PREGNANT WOMEN WITH CANCER

CHEMOTHERAPY IN PREGNANCY: FROM FETAL SAFETY TO MATERNAL EFFICACY

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Voor Nicolas, Marcus en Rosanne

Voor Moeke en Oma

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Supplementary data:

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Samenvatting

ACHTERGROND EN PROBLEEMSTELLING

Het internationaal netwerk over kanker, vruchtbaarheid en zwangerschap (INCIP) ontstond vanuit de zeldzaamheid van het samen voorkomen van kanker en zwangerschap. Bij een kankerdiagnose tijdens de zwangerschap, wordt de oncologische en verloskundige behandeling uitgedaagd door de bezorgdheid over de algemene gezondheid en prognose van zowel de moeder als het ongeboren kind. Een oncologisch behandelplan volgens de algemene zorgstandaarden voor niet-zwangere vrouwen is geadviseerd om de prognose van de moeder te beschermen. In de loop der jaren zijn er verschillende geruststellende publicaties over verloskundige en neonatale uitkomsten na kankerbehandeling tijdens de zwangerschap. Als gevolg hiervan is de behandeling van zwangere kankerpatiënten geëvolueerd, waarbij waar mogelijk oncologische behandeling wordt aangeboden, in plaats van een zwangerschapsafbreking of uitstel van behandeling tot na de bevalling. Zwangere kankerpatiënten lopen risico op ongunstige verloskundige uitkomsten, zowel direct door de kankerbehandeling als indirect door de fysieke impact en psychologische stress. Populatiestudies hebben een verhoogd risico aangetoond op zwangerschapsafbreking, doodgeboorte, vroeggeboorte (zowel spontaan als gepland), laag geboortegewicht en neonatale sterfte bij door kanker gecompliceerde zwangerschappen. De beschikbare literatuur ontbreekt echter aan informatie over de exacte impact van prenatale behandeling. De toediening van chemotherapie tijdens de zwangerschap is echter niet zonder risico's. Allereerst passeert chemotherapie de placenta en kan het de ontwikkeling en groei van de foetus beïnvloeden. Eerder onderzoek was gericht op het voorkomen van een laag geboortegewicht voor de zwangerschapsduur (SGA), zonder informatie over foetale groeirestrictie (FGR), gedefinieerd als foetussen die hun groeipotentieel niet bereiken. FGR wordt prenataal gediagnosticeerd via echografie en is een meer betrouwbare uitkomst met betrekking tot de neonatale risico's op korte en lange termijn, in vergelijking met SGA. Een belangrijk tweede argument voor bezorgdheid zijn de fysiologische veranderingen tijdens de zwangerschap, die leiden tot chemodilutie en zo mogelijks een verminderde werkzaamheid van chemotherapie. Het DOEL van dit doctoraat is om de veiligheid voor de foetus en de maternale uitkomst na kankerbehandeling tijdens de zwangerschap verder te onderzoeken.

ONDERZOEKSOPZET

Het uitbreiden van de INCIP database maakte het mogelijk om subanalyses te maken met betrekking tot de verloskundige en neonatale uitkomst per kanker- of behandelingstype. We voerden een eindanalyse uit van de verloskundige en neonatale uitkomsten van vrouwen met een primaire of recidiverende invasieve kankerdiagnose tijdens de zwangerschap of vrouwen die zwanger werden tijdens een kankerbehandeling tussen 1996 en 2021 (n=2172). Logistische regressiemodellen werden gebruikt om de evolutie van behandeling en de uitkomsten in de loop van de tijd te beoordelen, alsook de specifieke factoren voor

ongunstige verloskundige en neonatale uitkomsten te bepalen. Ontbrekende data werden opgevangen via meervoudige imputatie. Voor de analyses van foetale groei werd prenatale seriële echografische informatie verzameld. Voor overlevingsanalyse van Hodgkin-lymfoom selecteerden we niet-zwangere controlepatiënten uit de Universitaire Ziekenhuizen van Leuven, Rotterdam en Groningen, gematcht met INCIP-casussen op basis van stadium, leeftijd en periode bij lymfoomdiagnose. Voor borstkanker werkten we samen met de German Breast Group (GBG) en voerden we multivariabele Cox Hazard Regression-analyse uit, rekening houdend met prognostische factoren voor borstkanker.

RESULTATEN

Over het algemeen lopen vrouwen met kanker risico op vroegtijdige arbeid, spontane en geplande vroeggeboorte en groeivertraging van de foetus (hoofdstuk 1 en 6). Het toedienen van antenatale chemotherapie verhoogt deze risico's nog meer. Bij deze populatie wordt een voldragen bevalling aangemoedigd om een optimaal resultaat voor het kind te verzekeren, aangezien vroeggeboorte een belangrijke risicofactor is voor een verminderde neurocognitieve uitkomst. Echter, in afwachting van een al dan niet geplande aterme bevalling, is er een risico op spontane vroegtijdige arbeid. Andere risicofactoren voor vroegtijdige arbeid die in dit proefschrift zijn geïdentificeerd zijn gemetastaseerde en hematologische aandoeningen (hoofdstuk 1).

Observationele gegevens over verloskundige en neonatale uitkomsten van geregistreerde zwangere vrouwen met Hodgkin lymfoom, non-Hodgkin lymfoom, urologische kankers en maagkanker werden gepubliceerd en vormen een leidraad voor artsen en hun patiënten bij het bespreken van het klinische beleid (hoofdstuk 2). Dit proefschrift bouwt voort op het bewijs dat chemotherapie tijdens de zwangerschap geen aangeboren afwijkingen veroorzaakt, zolang het na 12 weken zwangerschap wordt toegediend (hoofdstuk 3). We beschreven de uitkomsten van vrouwen met oncologische chirurgie en tonen de mogelijkheid van het gebruik van G-CSFF tijdens de zwangerschap (hoofdstuk 4 en 5).

Foetale groeivertraging komt vaak voor bij zwangere kankerpatiënten (hoofdstuk 6). Kankerstadium (gemetastaseerde ziekte), kankertype (hematologische kanker), een lage gewichtstoename van de moeder tijdens de zwangerschap, hypertensie en roken spelen een rol. De vroegere zwangerschapsduur bij de diagnose van kanker is sterk gerelateerd aan een lager geboortegewichtpercentiel. Dit proefschrift suggereert een direct dosis-respons effect van chemotherapie op het neonatale geboortegewicht (hoofdstuk 1).

We bevestigen dat de algehele prognose van de moeder bij borstkanker en Hodgkin-lymfoom niet lijkt te worden beïnvloed door zwangerschap, ook niet wanneer chemotherapie tijdens de zwangerschap wordt gegeven (hoofdstuk 7 en 8).

CONCLUSIE

De resultaten van dit proefschrift ondersteunen de huidige klinische praktijk om zwangere vrouwen met kanker zoveel mogelijk te behandelen volgens de zorgstandaarden die worden aanbevolen voor niet-zwangere vrouwen. Chemotherapie tijdens de zwangerschap voor borstkanker en Hodgkin lymfoom lijkt geen invloed te hebben op de overleving van de moeder. De vooruitgang die we hebben geboekt door het behouden van de zwangerschap bij een kankerdiagnose, is geassocieerd met een verhoogd risico op ongunstige verloskundige uitkomsten (spontane vroeggeboorte en foetale groeivertraging). Kennis van risicofactoren, waaronder het gebruik van chemotherapie, het kankerstadium en de algemene mentale en voedingsstatus van de moeder, is cruciaal en we moedigen aan om de opvolging door een ervaren multidisciplinair team te organiseren. De zorg voor zwangere kankerpatiënten vereist inderdaad voortdurend een afweging van maternale en foetale belangen en risico's.

Summary

BACKGROUND

The rarity of cancer and pregnancy hampering research, resulted in the arise of an International Network on Cancer, Infertility and Pregnancy (INCIP). When cancer coincidences with pregnancy, the oncological and obstetric management is challenged by concerns on general health and prognosis of both the mother and the unborn child. Whenever possible, an oncological treatment plan according to the general standards of care for non-pregnant women should be offered in order to preserve maternal prognosis. Over the years, re-assuring reports on obstetric and neonatal outcomes following cytotoxic treatment during pregnancy are published. As a result, the management of pregnant cancer patients has shifted, offering cancer-specific oncological treatment depending on the gestational age whenever possible, instead of pregnancy termination or treatment delay until after delivery. Pregnant cancer patients are at risk of adverse obstetric outcomes, both directly through cancer treatment and indirectly by maternal physical and psychological stress. Population-based studies have shown an increased risk of pregnancy termination, stillbirth, preterm birth (both spontaneous and elective), small for gestational age (SGA) neonates and neonatal death in pregnancies complicated by cancer, however, they often lack information or power on the exact impact of antenatal treatment. The use of chemotherapy during pregnancy does raise two main issues. First of all, chemotherapy crosses the placenta and can impact fetal development and growth. Previous research focused on the occurrence of small for gestational age (SGA) neonates, however lacked information on fetal growth restriction (FGR), defined as fetuses who do not reach their growth potential. FGR is diagnosed prenatally and is a more reliable outcome regarding to the neonatal risks on short- and long-term, compared to SGA. An important second concern are gestational physiological changes resulting in chemodilution and a plausible reduced drug efficacy of chemotherapy. In this Phd we AIMED to further investigate and build evidence regarding the fetal safety and maternal outcome following cancer treatment during pregnancy.

METHODOLOGY

We expanded the INCIP registry in order to enlarge the numbers enabling sub-analyses with regard to obstetric and neonatal outcome per cancer or treatment type. We performed a final analysis of women with a primary or recurrent invasive cancer during pregnancy or women who conceived while receiving invasive cancer treatment between 1996 and 2021 (n=2172). Logistic regression models were used to assess evolution of management and outcomes over time, specific factors for adverse obstetric and neonatal outcomes and the association between prognostic factors and small for gestational age (SGA). Where applicable, multiple imputation was used for missing values. For the analyses of fetal growth, prenatal serial scan information was collected. For survival analysis of Hodgkin lymphoma we selected non-pregnant control patients from the University Hospitals of Leuven, Rotterdam and Groningen, matched on stage, age, period at diagnosis with

INCIP cases. For breast cancer, we collaborated with the German Breast Group (GBG) and we performed multivariable Cox Hazard Regression analysis, accounting for prognostic factors of breast cancer.

RESULTS

Overall, women with cancer are at risk of preterm onset of labor, preterm delivery and fetal growth restriction (chapter 1 and 6). The administration of antenatal chemotherapy even more increases the risk. A term delivery is encouraged in this population, to assure an optimal outcome for the child, as prematurity is a major risk factor for impaired neurocognitive outcome. As a counterpart, while awaiting term delivery in this high risk population, there is an increased risk of preterm onset of labor. Other risk factors identified in this thesis for preterm onset of labor are metastatic and hematological disease (chapter 1).

Observational data on obstetric and neonatal outcomes of registered pregnant women with Hodgkin lymphoma, non-Hodgkin lymphoma, urological cancers and gastric cancer were published to guide physicians in clinical management (chapter 2). This thesis builds further on the evidence that chemotherapy during pregnancy does not induce congenital malformations, as long as it is administered after 12 weeks of gestation (chapter 3). We observed the outcomes of women with oncological surgery and G-CSF during pregnancy (chapter 4 and 5).

Fetal growth restriction is common in pregnant cancer patients (chapter 6). Cancer stage (metastatic disease), cancer type (hematological cancer), maternal weight gain during pregnancy, maternal hypertension and smoking play a role. An early gestational age at cancer diagnosis is strongly related to lower birthweight percentiles. In this thesis, we showed that there appears to be a direct dose-response effect of chemotherapy on neonatal birthweight (chapter 1).

We confirm that overall maternal prognosis in breast cancer and Hodgkin lymphoma appears unaffected by pregnancy, also when chemotherapy is given during pregnancy (chapter 7 and 8).

CONCLUSION

Results of this thesis support the current clinical practice of treating pregnant women with cancer by the standards of care recommended for non-pregnant women as much as possible. Chemotherapy in pregnancy for breast cancer and Hodgkin lymphoma does not seem to impact maternal survival. The undoubtedly progress we made in preserving the pregnancy when at the same time cancer is diagnosed, is associated with an increased risk of adverse obstetric outcomes (spontaneous preterm delivery and fetal growth restriction). Knowledge of risk factors including the use of chemotherapy, cancer stage and maternal general health and nutritional status is crucial to tailor and organize the obstetric follow up by an experienced multidisciplinary team. Indeed, care for pregnant cancer patients continuously requires balancing of maternal and fetal benefits and risks.

Part I - INTRODUCTION

Partly adapted and updated from Maggen *et al.,* 2019[1]

Management of cancer during pregnancy and current evidence of obstetric, neonatal and pediatric outcome: a review of the literature

Charlotte Maggen, Mathilde Van Gerwen, Kristel Van Calsteren, Tineke Vandenbroucke, Frédéric Amant

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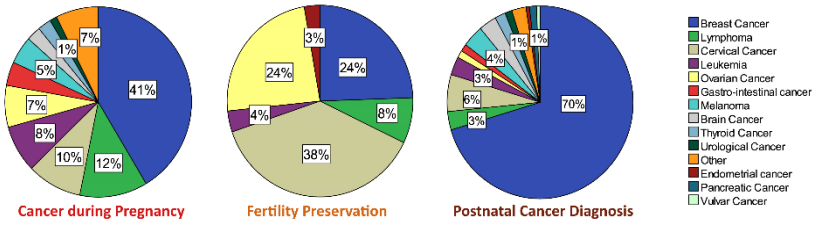
When a cancer diagnosis coincidences with a pregnancy, physicians are confronted with a major treatment dilemma, balancing fetal safety and maternal risks. It is highly important to address the feasibility and safety of oncological treatment during pregnancy in order to inform these patients about the possible risks for both mother and child. Historically, most evidence is derived from observational data, as the rarity of cancer during pregnancy and so-called ethical considerations limit conducting clinical trials in this population.

I. History of the research team

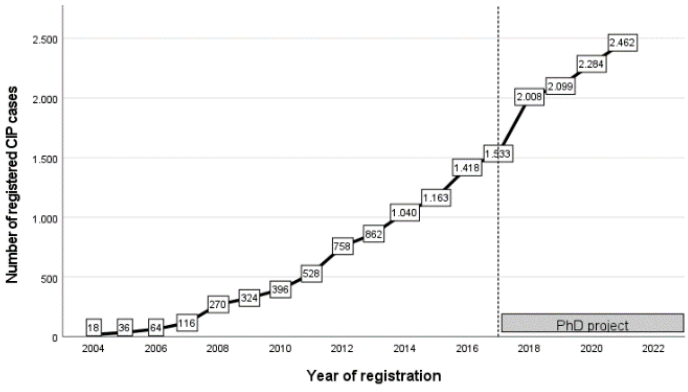
In 2005, inspired by a young pregnant patient with cervical cancer who was desperate to keep her pregnancy, a medical team from the University Hospitals of Leuven launched a research group on 'Cancer in Pregnancy'. The lack of knowledge encouraged the team to start a unique registry that combines both oncological and obstetric data of women with a cancer diagnosed during pregnancy, registered both retrospectively as prospectively (from 2005, with informed consent). Also research projects on the long-term effects of in utero cancer treatment, placental effects and trans-placental transfer of chemotherapy were included (PhD of Kristel Van Calsteren, Mina Mhallem Gziri, Sileny Han, Magali Verheecke, Tineke Vandenbroucke, Jorine de Haan and Jeroen Blommaert).

Figure 1: Overall distribution of cancer types in the INCIP registry



Over the years, the research group expanded and gained more international interest, with the support of the European Society of Gynecological Oncology (ESGO). The research focus was extended with 'fertility in young women with cancer', 'postpartum (breast) cancer diagnosis' and 'psychological impact and coping of a cancer diagnosis during pregnancy'. In 2014 the 'International Network of Cancer, Infertility and Pregnancy" (INCIP) was formed.[2] Nowadays this network consists of 63 participating hospitals from 25 countries, which are all compliant with the INCIP study protocol (Table S-INCIP). Besides collaborating in research projects, within this network meetings are organized to brainstorm on new research topics and discuss ongoing research. Moreover international guidelines are published together.[3-5] The international network allows collaboration with other networks, like the German Breast Group (GBG). This PhD thesis forms part of the INCIP study project and further builds on current evidence on cancer during pregnancy by analyzing the INCIP database (Figure 1 and 2, Figure SI.1).

Figure 2: Overview of number of registered cases 'Cancer in pregnancy' (CIP) over the years.



II. Current evidence on cancer during pregnancy

Epidemiology

The epidemiology of a cancer diagnosis during pregnancy is challenging to study as nationwide registries do not usually combine both obstetrical and oncological data, resulting in a likely underestimation of the incidence of cancer-related miscarriages or abortions. Also, population-based studies differ in inclusion criteria, often incorporating postnatal cancer diagnoses. Furthermore, differences in the denominator used (pregnancies or live births) may lead to variation in reported incidence rates between studies. Hence, population-based studies reporting on the incidence of cancer during pregnancy, report incidence rates of 17-34 per 100,000 live births and 21-38 per 100,000 pregnancies.[6-18] Incidences reported for the most common cancer types diagnosed in pregnancy, based on recent data, are represented in Table 1.[6-31] With the increasing trend to postpone childbirth to a later age, the incidence is expected to rise. More performant screening tools in general obstetrical care resulted in the diagnosis of asymptomatic cancers (prenatal ultrasound, genome-wide Non-invasive Prenatal test (NIPT), cervical cancer screening by the pap and Human Papillomavirus (HPV) test).[32-34]

Table 1: Incidences of Cancer diagnosis during pregnancy (per 100,000 pregnancies or births) reported by population-based studies.

Malignancy	Range of number of CIP cases included	Incidence (cases/ 100,000 pregnancies)	Incidence (cases/ 100,000 births)
All cancer types	186-13930	21.9-38.1[8-10,13,17]	17.3-34.1[11,12,14-16,18,35]
Breast Cancer	28-722	3.7-7.7[9,10,13,17]	3.1-10.5[11,12,14,16,28,31,35]
Cervical cancer	17-231	1.4-5.1[9,10,13,17]	2.5-4.6[11,12,14,16,21,35]
Melanoma	9-304	1.9-15.1[9,10,13,17]	1.4-14.9[12,14,16,26,35]
Hodgkin lymphoma*	15-638	N/A	0.7-8.1[11,24,35]
Non-Hodgkin lymphoma	58-427	N/A	1.2-5.4[25,35]
Leukemia	6-291	0.6[13]	0.4-2.4[11,16,29,35]
Ovarian Cancer	8-171	1.2-1.8[9,13,22]	1.2-3.7[11,12,14,16,27,35]
Ovarian masses with low malignant potential (Borderline)	87-115	2.4[22]	1.1[27]
Thyroid cancer	17-174	2.3–3.2[9,13]	0.8-4.2[11,12,14,16,20,35]
Brain tumor	4-70	0.9-1.1[9,13]	0.6-1.4[12,16,35]
Colorectal cancer	3-106	0.6-0.8[9,13]	0.6-2.6[11,12,23,35]

* Large variation in reported cases due to geographical and reporting differences. El Messidi (incidence 8.4/100,000): Given the population-based design of the study with a large number of incident cases (n=638) of Hodgkin lymphoma in pregnancy, the pooled samples likely estimate the true incidence of the disease diagnosed in pregnancy.
Haas et al. (1985) was excluded from this overview: Overall, reported incidences (of all cancer types, breast cancer, melanoma, Hodgkin lymphoma, Leukemia, Ovarian cancer, Brain tumor and colorectal cancer) were lower compared to more recent publications, possible explained by underreporting or underdiagnoses of cancer. The reported higher incidence of cervical cancer during pregnancy in Haas et al. (11.0/100,000) might be explained by the introduction of screening for cervical cancer during the study period.

Melanoma, breast cancer, hematological cancers, thyroid cancer and gynecological cancers are the most frequently diagnosed cancers during pregnancy, mirroring the distribution in premenopausal women.[36] Besides genetic predispositions (such as BRCA mutation carriers), typical risk factors for cancer in young women are carcinogens such as ultraviolet (UV) light, smoking, drugs and human immunodeficiency virus (HIV).[37] Western lifestyle changes explain a rise in the incidence of obesity-related cancers (eg. colorectal, gallbladder, pancreatic, uterine cancer) in young adults.[38] Older maternal age, high socio-economic status, multi-parity independent of maternal age, multiple pregnancy and prior diagnosis of cancer are retained as risks factors for an oncological diagnosis during pregnancy.[9,13,20]

Treatment options during pregnancy

In the past termination of pregnancy or delaying treatment until postpartum were the advised options, based on fear for the potential toxic effect of chemotherapy and radiotherapy on the unborn child. This resulted in the loss of wanted pregnancies and impairment of the maternal prognosis by delaying cancer therapy. In the management of cancer during pregnancy the key principle is that the same treatment as non-pregnant patients should ideally be offered. However, from the fetal perspective some treatments are not advised or even contra-indicated during pregnancy. (Pre-)clinical research from the last 20 years revealed that certain cytotoxic treatment options can be considered during certain phases of pregnancy. The decision to continue or stop the pregnancy, and which type of treatment is given, depends on the tumor (sub)type, stage, tumor biology and prognostic markers, maternal prognosis, gestational age at diagnosis and wish of the future parents with regard to the pregnancy.

Termination of pregnancy remains an option in early pregnancy, especially for advanced cancers. In order to safeguard maternal prognosis, initiation of cancer treatment in pregnancy should be considered, especially when pregnancy preservation is preferred and cancer is diagnosed in the first half of pregnancy. Of note, toxic events during the periconceptional period might affect early embryogenesis and result in a miscarriage, whereas subsequent toxic exposure might interfere with the formation of organs, with the most susceptible period occurring between 2 and 8 weeks after conception (between 4 and 10 weeks post-menstruation).[39] In late pregnancy the fetal risks of prenatal cancer treatment (most important impaired fetal growth and spontaneous preterm delivery, cfr below) should be balanced against the option of planned delivery in order to initiate cancer treatment postpartum, taking into account that prematurity is a major determinant for impaired pediatric outcome.[40] Due to a shortened period of in utero organ development, morbidity and mortality is higher in premature infants and the risk of respiratory, cardiac, renal, and endocrine system disorders later in life is higher compared to infants born at term.[41] Preterm born infants have immature brain development affecting neurodevelopment (cognitive and behavioral functioning; language delay, autism, anxiety) on the short and long-term.[42-44] A dose-response effect of prematurity is suggested, with poorer

health outcomes with decreasing gestational age at birth.[45,46] Delivery after 34 weeks of gestation and ideally after 37 weeks of gestation should be intended.

Chemotherapy crosses the placenta and has the potential to influence fetal development and growth directly.[39] Chemotherapy is contra-indicated in the first trimester because it can potentially disturb organogenesis and is associated with miscarriage, fetal death and congenital malformations.[47] The ability of chemotherapy to cross the placenta is defined by the physicochemical properties of the drugs such as lipid solubility and ionization constant, molecular weight and protein binding. Due to the relatively low molecular weight, most cytotoxic drugs can cross the placenta. However, the placenta acts as a barrier and the exposed fetal concentration is substantially lower than the maternal concentration.[48-51] Some chemotherapeutics carry more risks than others. The current evidence on placental passage and neonatal risks for several types of chemotherapy most commonly used during pregnancy is summarized in Table 2. The placenta acts as a barrier, but also facilitates clearance of cytotoxic drugs. Therefore, a safety interval of two or three weeks, depending on the chemotherapy regimen, between the last administration of cytotoxic drugs and delivery is advised to reduce the risk of hematopoietic suppression in the neonate.[52] Chemotherapy-induced weakening of the amnion-chorion membrane may play a direct role in the association of prenatal chemotherapy and preterm spontaneous labor. [25,53-55]

Table 2: Current evidence on possible neonatal risks after prenatal exposure starting from the second trimester of pregnancy to most frequently used cytotoxic drugs

Drug class	Drug	Transplacental passage *	Neonatal risk (OR (95% CI))	Specific recommendation for neonatal follow-up	Reference
Platinum compounds	Carboplatin, (Cisplatin)	± 60%	- **SGA** (OR 3.12 (1.45 – 6.70)) Risk of ototoxicity greater for cisplatin; use carboplatin in preference - NICU admission OR 1.66 (0.77-3.55)	Postnatal auditory test	[49], [51], [100]
Alkylating agents	Cyclophosphamide	± 20%	- SGA (OR 2.08 (0.88-4.91)) - NICU admission OR 0.88 (0.46-1.70)		[48], [51], [100]
Antimetabolites	5-Fluorocil	± 28%	- SGA (OR 1.24 (0.70 – 2.22) - NICU admission OR 1.03 (0.60-1.74)		[50], [51], [100]
Antitumour antibiotics	Epirubicin	<10%	- SGA (OR 0.50 (0.21 – 1.22) - NICU admission OR 1.21 (0.62 - 2.38)	Postnatal fetal echocardiography	[48], [51], [100]
	Doxorubicin	<10% (active metabolite)	- SGA (OR 0.50 (0.21 – 1.22) - NICU admission OR 1.21 (0.62 - 2.38)	Postnatal fetal echocardiography	[48], [51], [100]
Taxanes	Paclitaxel, docetaxel	<2%,	Accumulation in neonatal tissue is feared. - **SGA** (OR 2.07 (1.11 – 3.86) - **NICU admission** OR 2.37 (1.31- 4.28)		[49], [51], [100]
Vinca Alkaloids	Vinblastin	± 20%	- **SGA** (OR 2.34(1.04-5.25) - NICU admission OR 1.63 (0.78-3.38)		[48], [51], [100]

SGA: small for gestational age
NICU: Neonatal Intensive Care Admission
*Values estimated from reported data in literature

Surgery can be performed safely during the pregnancy, as long as some anesthetic and surgical adjustments are made.[1,56,57] In the postoperative setting, prevention of thromboembolism with low molecular weight heparin is indicated because of the hypercoagulable state of pregnancy and cancer.[58]

Antihormonal treatment should ideally be avoided during pregnancy. Tamoxifen appears to be associated with intra-uterine fetal death and birth defects (12.6% in contrast to 3.9% in the general population).[59] However the causal relationship is not established. Patients should be counseled on the maternal oncological risks of discontinuing tamoxifen because of a pregnancy wish and the fetal risks of exposure to tamoxifen in pregnancy.[60] Over the years, *targeted therapy* is more developed and is now used in the treatment of several types of cancers. The use of targeted therapy in pregnant patients is often discouraged because of the limited experience in pregnancy. Using these drugs may be associated with fetal anomalies as specific molecular changes in cancer development are targeted, which may also be mechanisms in fetal development. IgG molecules are actively transported in the placenta by receptor mediated endocytosis, from the second trimester onwards. Table 3 gives a brief overview of current evidence on neonatal risks when targeted therapy or tamoxifen is used during pregnancy.[59-64]

Whether or not *radiation therapy* should be started in pregnancy is always a dilemma and the potential risks and benefits should extensively be discussed with the pregnant patient and her partner. Pelvic irradiation, with direct effect on the fetus, should never intentionally be performed during pregnancy. For the upper body (eg. breast, brain) the total fetal exposure should always be calculated by a physicist using a phantom model and ideally should not exceed 0.1 Gy.[65] Fetal and neonatal risks include congenital malformations, mental retardation, cataract and childhood cancer.[66]

Besides these direct mechanisms of cancer treatment, adverse obstetric effects of cancer will also be mediated indirectly by secondary maternal physical and psychological stress.[43,67] Cancer-related mental health problems (depression, anxiety) are suggested to be an independent risk factors for adverse obstetric outcomes (low neonatal birthweight, SGA and preterm delivery).[68] Stress of a cancer diagnosis may potentially activate the maternal hypothalamic-pituitary-adrenal axis, provoking labor by the release of oxytocine.[69] Pain may provoke preterm uterine contractions. General cancer-mediated inflammation will cause a cytokine release, with the potential to contribute to preterm spontaneous labor.[70] Chemotherapy results in hematological suppression and malnutrition (by nausea and vomiting), both maternal risk factors for fetal growth restriction.[71,72] Maternal stress and depression are risk factors for malnutrition and are also suggested to affect fetal growth.[73] Oxidative stress may damage placental function, thereby impacting fetal growth.[74]

Table 3: Current evidence on possible neonatal risks after prenatal exposure to targeted therapy and tamoxifen

Drug	Function	Cancer type	Neonatal Risk	Recommendation for use during pregnancy	Ref.
Trastuzumab	Her2-receptor inhibitor	breast cancer, gastric cancer	oligohydramnios, hypoplastic lungs and fetal death by its ligation to HER2-receptors that are present in the renal epithelium of the fetus	Not to use	[61], [199]
Imatinib	Tyrosine kinase inhibitor	chronic myeloid leukemia	Exposure in first trimester associated with congenital malformations (11% of exposed fetuses) and spontaneous abortion. Safety data for exposure in second or third trimester are limited but no major minor congenital malformations are reported	To use with caution	[62], [64], [199]
Rituximab	Anti CD20 monoclonal antibody	non-hodgkin lymphoma	Neonatal cytopenia, no congenital malformations reported. Potential maternal benefits should be outweighted against limited fetal risks.	To use with caution	[63], [199]
Interferon-α	Pleiotropic cytokine	melanoma, CML, lymphoma, hairy cell leukemia and AIDS-related Kaposi sarcoma	Dose-dependent increased abortion rate in animal models. Limited placental transfer. 1 case reported with congenital malformations (exomphalos, right renal agenesis, and hemivertebrae), out of 43 cases, 2%).	To use during pregnancy	[64], [199]
EGFR inhibitors: erlotinib, gefitinib, afatinib and cetuximab	EGFR is involved in cell proliferation and differentiation and has been implicated in various stages of embryonic development	(metastatic) lung cancer	Limited data. Increased risk of abortion in animal models. 3 cases with erlotinib during pregnancy revealed no congenital malformations. More safety data is needed.	Not to use	[199]
Anti-angiogenetic agents: bevacizumab (1), sorafenib (2), sunitinib (3)	Vasculogenesis and angiogenesis in the human placenta and for normal fetal development	Advanced stage solid tumors (1), Renal cell carcinoma (RCC), thyroid cancer and liver cancer (2), advanced RCC	Embryo-fetal death, (skeletal) congenital malformations in animal models. No human data for sorafenib and sunitinib. Intraveal injections of bevacizumab was not associated with adverse events.	Not to use	[199]
BRAF-inhibitor: Vemurafenib	Inhibition of BRAF, proto-oncogen	Advanced melanoma	Limited data. No teratogenesis reported in animal models. One case report initiated at 25 weeks of gestation and low birth weight.	Not to use	[199]
Tamoxifen	Selective oestrogen receptor modulator	Breast cancer	Intra-uterine fetal death and birth defects like Goldenhar syndrome (oculo-auriculo-vertebral dysplasia), ambiguous genitalia and Pierre Robin sequence (triad of small mandible, cleft palate and glossoptosis.	Not to use	[59], [60]

Obstetric outcome

Most information on obstetric risks for cancer patients comes from large population based or large multicenter cohort studies, summarized in Table 4 (a comprehensive list) and Table SI.1 (describes reported outcomes).[7,9,12,13,15-31,35,39,54,75-100] Often these studies lack information on treatment modalities during pregnancy, hampering adjustment for cancer treatment in analyzes of adverse pregnancy outcomes.

The largest INCIP study to date revealed a pregnancy result, based on 1089 singleton pregnancies with known obstetric outcome, as follows; 1% still birth, 2% miscarriage, 9% termination of pregnancy and 88% live birth.[100] The main reasons for termination were start of oncological treatment or poor maternal prognosis (77%), unwanted pregnancy (11%), and fetal anomalies (4%). Patients were mostly diagnosed during the second

trimester of pregnancy (48%). In total, 429 (37%) patients were treated with chemotherapy during pregnancy. Of the 969 ongoing singleton pregnancies, seven (1%) intrauterine fetal deaths and seven (1%) perinatal deaths were reported. PPROM (preterm premature rupture of membranes) or preterm contractions (10%) were the most frequently reported obstetric complications among ongoing singleton pregnancies. Half of the deliveries were preterm (48%), of which 88% were iatrogenic for oncological or obstetric reasons and 12% were spontaneous (for those with available data). A change in management over time, with more patients treated during pregnancy resulting in more live births was observed. Every 5 years there was, on average, an increased likelihood of livebirth among singleton pregnancies (RR 1·04, 95% CI 1·01–1·06), a reduction in the risk of preterm livebirth (0·93, 0·86–0·99), and a reduction in the risk of iatrogenic preterm livebirth (0·91, 0·84–0·98). In line with the decrease in preterm deliveries, NICU admissions decreased (RR 0·91, 95% CI 0·83–0·99) and PPROM or preterm contractions decreased (0·97, 0·80–1·18) every 5 years, whereas the risk of small for gestational age (SGA) increased (1·16,0·99–1·35).

Spontaneous preterm labor can be caused directly by cancer (treatment) or inflammation, and indirectly by pain and maternal stress (cfr above).[54,100] Maternal deterioration, optimal timing of cancer treatment or the need to start with therapy that is not compatible with pregnancy may force *iatrogenic preterm delivery*.[7,9,53] The *cesarean section* rate in patients with a cancer diagnosis during pregnancy appears to be higher compared to the normal population.[9] This is likely to reflect the standard management of certain types of cancer (eg. cervical cancer), but may also be attributed to the comfort of a planned, controlled delivery. Other medical and obstetrical complications frequently reported in population-based studies are venous thromboembolism, maternal sepsis, blood transfusion, postpartum hemorrhage and pre-eclampsia, however none of these studies assessed the impact of antenatal chemotherapy. [9,18,21-29,35,92,96,97,99]

Pregnant cancer patients might have multiple morbidities affecting *fetal growth*, including antenatal chemotherapy, a high maternal age, stage of disease or organ dysfunction, low maternal BMI or poor nutritional status, co-medications and cancer-related stress. Current literature on this topic is conflicting: some of the studies examining the effects of cancer during pregnancy on fetal growth do not show an association between a cancer diagnosis and *SGA*[9,15-17,80,82,92,101], whereas others do.[12,18,89,94,100] Fetal exposure to chemotherapy has been associated with SGA in some studies[4,12,100], whereas other studies only found a negative impact of antenatal chemotherapy on birthweight, but not necessarily leading to SGA.[16,17] Conflicting data are the result of differences in the used definitions. Of note, studies on cancer and neonatal birthweight are inconsistent in the outcome that is studied: low birthweight (birthweight below 2500g), SGA or fetal growth restriction (FGR), defined by fetuses who do not reach their growth potential. Interestingly, few data are available on the real incidence of FGR. The diagnosis of FGR is assessed prenatally, based on prenatal ultrasound by fetal growth and Doppler studies. [102] This distinction is highly important, because FGR infants are at risk of perinatal morbidity and impaired long-term health outcome.[103] The definition of SGA includes

constitutional healthy SGA fetuses with normal outcomes, however misses fetuses with growth problems but with a birthweight within normal limits.[104] Future research on cancer and fetal growth should focus on prenatal fetal growth assessment by ultrasound. Fetal growth is influenced by placental, maternal and fetal factors.[71] Only the INCIP research and a recent paper of Freret et al. assessed, besides antenatal chemotherapy, other contributing risk factors for SGA or low neonatal birthweight.[98,100] Freret et al. focused on the neonatal birthweight in a small cohort of 74 breast cancer patients receiving antenatal chemotherapy. In the adjusted model (taking into account smoking and hypertension), chemotherapy exposure was associated with lower birthweight (Δ z-score of -0.49, p=0.03), but similar rates of SGA (8.2 vs. 8.0%, p= 1.0; Fisher's exact test).[98] Duration of chemotherapy exposure nor exposure to taxanes did impact neonatal birthweight. The largest cohort study to date on CIP patients (n=1170, 955 included for SGA analysis) showed an association between chemotherapy and SGA neonates, with the greatest risk for platina and taxanes.[100] Another risk factor was a higher maternal age at cancer diagnosis. An important limitation of current research is the inability to distinct between SGA and FGR.

The literature is inconsistent regarding the association of cancer during pregnancy and *stillbirth* or *neonatal death*. Most population-based linkage studies found no increased risk.[9,19,20,24,25] A recent large Swedish nationwide cohort study, lacking information on antenatal management, concluded that maternal cancer diagnosis was associated with an increased risk of preterm SGA birth, stillbirth and neonatal mortality.[12] Also postnatal cancer diagnosis was found to be associated with preterm SGA and neonatal mortality, but not with stillbirth. The association between SGA and stillbirth is not surprising as they share etiological factors, including intrauterine malnourishment[105] and SGA itself is a major determinant of stillbirth, especially preterm stillbirth.[106] The increased risk of neonatal mortality among these pregnancies could be explained by the high incidence of preterm birth, a leading cause of neonatal death.[107] Furthermore cancer during pregnancy seems to be associated with *Neonatal Intensive Care Unit (NICU)* admission. In the most recent cohort study, 41% of neonates was admitted to NICU, and in 84% of cases this was related to prematurity.[100] NICU admission was associated with exposure to taxanes and was more likely after a diagnosis of gastrointestinal or cervical cancer during pregnancy.

Maternal death is increased in pregnant women with cancer compared to non-cancer pregnant controls.[7,18,25,29,35,88,97,99] Only one study further specified the risk of maternal death according to cancer type [data of only 84 women: (highest rate seen with lung cancers (66.7%), followed by gastrointestinal (50.0%), central nervous system (50.0%), hematologic cancers (30.8%)].[88]

Table 4: Overview of population-based studies and large (>50) cohort studies reporting on obstetric and neonatal outcomes in pregnant cancer patients (n=50)

Author, year	Cancer type	N. of cases	Country	Pro – or retrospective	Cohort or population-based study
Sullivan et al., 2022[31]	Breast Cancer	40	Australia and New-Zealand	Pro	Population based
Freret et al., 2022[98]	Breast cancer	74	USA, Boston	Retro	Single center cohort
Matsuo et al., 2022[99]	All types	10151	USA, NIS	Retro	Population based
Ma et al., 2022[18]	All types	13930	USA, NIS	Retro	Population based
Landtblom et al., 2022[30]	MPN	342	Sweden	Retro	Population based
Greiber et al., 2022[17]	All types	1068	Denmark	Pro	Population based
Wu et al., 2021[97]	All types	39118	USA, NIS	Retro	Population based
Esposito et al., 2021[16]	All types	831	Italy	Retro	Population based
Barrois et al., 2021[95]	All types	71	France	Retro	Single center cohort
Greiber et al.,2021[96]	All types	1330	Denmark	Pro	Population based
Puzzi-Fernandes et al., 2020[94]	All types	66	Brazil	Retro	Single center cohort
Safi et al., 2019[93]	Breast Cancer	24	Australia and New-Zealand	Pro	Population based
Nolan et al., 2019[29]	Acute leukemia	291	Canada	Retro	Population based
Niu et al., 2019[92]	All types	707	USA,Washington	Retro	Population based
Shechter Maor et al., 2019[28]	Breast cancer	772	USA, NIS	Retro	Population based
De Haan et al., 2018[100]	All types	1170	INCIP	Pro + retro	Multicenter cohort
Momen et al., 2018[15]	All types	9598	Sweden and Denmark	Retro	Population based
Danet et al., 2018[91]	All types	75	France	Pro	Multicenter cohort
Sabeti Rad et al., 2017[90]	All types	790	Sweden	Retro	Multicenter cohort
Parazzini et al., 2017[13]	All types	1475	Lombardy, Italy	Retro	Population based
Lu et al., 2016[12]	All types	984	Sweden	Retro	Population based
Garofalo et al., 2017[89]	All types	59	Italy	Retro	Single center cohort
Shim et al., 2016[88]	All types	87	Korea	Retro	Single center cohort
Nazer et al., 2015[27]	Ovarian cancer	179	Canada	Retro	Population based
El Messidi et al., 2015[25]	NHL	427	Canada	Retro	Population based
Bannister-Tyrrell et al.,2015[26]	Melanoma	195	Australia	Retro	Population based
El Messidi et al.,2014[24]	Hodgkin lymphoma	638	Canada	Retro	Population based
Murthy et al., 2014[87]	Breast cancer	81	USA, Texas	Pro	Single center cohort
Meisel et al., 2013[86]	Breast cancer	74	USA, Boston	Retroe	Single center cohort
Evens et al., 2013[85]	Lymphoma	90	USA, Boston	Retro	Multicenter cohort
Lee et al., 2012[9]	All types	499	Australia	Retro	Population based
Loibl et al., 2012[54]	Breast Cancer	413	INCIP and GBG	Pro + retro	Multicenter cohort
Abdel Hady El et al., 2012[82]	All types	118	Egypt	Pro	Single center cohort
Aviles et al., 2012[83]	Hematological	54	Mexico	Pro+ retro	Single center cohort
Cardonick et al., 2012[84]	Breast + ovarian ca	129	USA, New Jersey	Pro	Multicenter cohort
Cardonick et al., 2010[81]	Breast cancer	130	USA, New Jersey	Pro	Multicenter cohort
Cardonick et al., 2010[80]	All types	231	USA, New Jersey	Pro	Multicenter cohort
Dahling et al., 2009[23]	colorectal cancer	134*	USA, California	Retro	Population based
Langagergaard et al., 2008[79]	Hodgkin Lymphoma	292	Denmark	Retro	Population based
Leiserowitz et al., 2006[22]	Ovarian masses	87	USA, California	Retro	Population based
Langagergaard et al., 2006[78]	Breast cancer	695	Denmark	Retro	Population based
Hahn et al., 2006[77]	Breast cancer	57	USA, Texas	Pro	Single center cohort

Dalrymple et al., 2005[21]	Cervical cancer	136	USA, California	Retro	Population based
Yasmeen et al., 2005[20]	Thyroid cancer	129	USA, California	Retro	Population based
O'Meara et al., 2005[19]	Melanoma	145	USA, California	Retro	Population based
Cardonick et al., 2004[39]	All types	55	USA, New Jersey	Pro+ retro	Multicenter cohort
Smith et al., 2003[7]	All types	4539	USA, California	Retro	Population based
Smith el al., 2001[35]	All types	2247	USA, California	Retro	Population based
Aviles et al., 2001[76]	Hematological ca	84	Mexico	Pro	Single center cohort
Ibrahim et al., 2000[75]	Breast cancer	72	Saudi Arabia	Retro	Single center cohort

Abbreviations: NIS: Nationwide Inpatient Sample; INCIP: International Network on Cancer, Infertility and Pregnancy; GBG: German Breast Group; Pro: prospective; Retro: retrospective; ca: cancer; MPN: myeloproliferative neoplasms; NHL: Non-Hodgkin lymphoma
INCIP studies published before the latest interimanalysis (de Haan et al., 2018) are excluded from the table, because of overlapping cases
*includes also cases diagnosed within 12months after delivery, numbers not further specified
** includes cancer diagnoses 2 years prior to pregnancy until birth, numbers not specified
*** includes also cancer diagnoses up to one year after delivery, numbers not further specified.

What is known on the impact on the child

In the short-term, outcome of children exposed to maternal malignancy and its treatment on general health, cardiologic, cognitive, behavioral and neurological development is reassuring.[43] Long-term follow-up is still ongoing. Table SI.2 gives an overview of the published series on prenatal cancer exposed children.[40,76,83,87,108-116]

The potential effect of malignancy and cancer treatment on fetal health is a concern. The effects of chemotherapy beyond the first trimester could potentially affect the development of the brain and the heart. The frontal functions of the brain (attention, memory, and executive functions) are most vulnerable to cytotoxic drugs in adults and children.[117] Anthracyclines, commonly used in the treatment of breast cancer and hematologic malignancies, are potentially cardiotoxic. To record the short- and long-term effects of cytotoxic drugs, children that were prenatally exposed to cancer treatment are followed in an international, multicenter study, integrated in the INCIP. The children are assessed with a general physical examination, cognitive testing and an evaluation of the heart function at regular time intervals (at birth, 18 months, 3 years and then every three years until the age of 18). The first results on 70 children with a median follow-up period of 22.3 months were re-assuring, indicating that general health and growth, and central nervous system, cardiac and auditory function of children born to mothers treated with chemotherapy during pregnancy did not differ from the general population.[111] During echocardiographic examination, no cardiac defects were identified and all cardiac dimensions were within the normal range. The ejection fraction, fractional shortening and interventricular septum thickness were slightly decreased in study versus control children. However, all measurements were still within the normal range. These reassuring results were confirmed in a large case-control study that compared the development of 129 exposed children to 129 healthy matched controls with a follow-up period of 36 months.[40] The incidence of preterm delivery in the prenatal-exposure group was 61.2%. Cognitive, cardiac and general development did not differ between both groups. However, the study concluded that prematurity was correlated with a worse cognitive outcome and this effect was independent of the cancer treatment. This is an important conclusion as an iatrogenic preterm delivery is common in the

management of pregnant patients to optimize the timing of their oncological treatment. A recent study of 132 children born to women with cancer, of whom 97 were exposed to chemotherapy, showed normal development at the age of 6 year.[113] However, subtle differences between these children and matched healthy controls were found in verbal intelligence in favor of the latter. Interestingly, in a post-hoc analysis, the difference of verbal intelligence was more distinct in the group of children who lost their mother to cancer. Hence, detection of verbal development delays and early psychosocial stimulation to prevent underdevelopment could be considered. In a group of 21 newborns exposed to anthracycline/cyclophosphamide-based chemotherapy in utero, no differences in fetal brain growth were found compared to a group of healthy controls.[118] However, a recent publication investigated the potential effects in the brain of 42 children prenatally exposed to cancer and/or chemotherapy by multimodal neuroimaging.[114] Although clinically not significant, subtle changes in grey and white matter structural development were identified, which definitively needs further investigation.

Ototoxicity is a known complication of platinum-based chemotherapy and cisplatin carries the greatest risk.[119,120] Cisplatin has a low molecular weight and has the potential to easily cross the placenta.[51] . Few cases of hearing loss after prenatally exposure to cisplatin have been reported.[121,122] Infection, the use of aminoglycosides and neurodevelopmental problems were possible confounding factors in reported cases.[111] This risk should be carefully weighed and follow-up of hearing after birth is recommended. Where possible, cisplatin should be replaced by carboplatin with a more favorable toxicity profile.

Other potential adverse effects of prenatal exposure to chemotherapy and/or radiotherapy are malignant disease and sub- or infertility in the children. [123] In a group of 84 chemotherapy-exposed children with a median follow-up of 18.7 years, no secondary malignancies were observed and 12 second-generation children were born.[76] However, more studies, larger samples and longer-term follow-up of children prenatally exposed to cancer treatment are needed to delineate the safety on secondary cancers and fertility.

What is known on the long-term maternal outcome

To date, there is no evidence that pregnancy impacts oncological prognosis as long as patients are managed according to standard treatment as much as possible.[4,8] However, this is still a subject of debate, as there are some remaining concerns. A decreased immunosurveillance as a result of the transient maternal immunosuppressive state secondary to placentation, may enhance tumor growth.[124] Also, it is plausible that the altered hormonal state might play a role in tumor progression.[125] Especially in potentially hormone-dependent cancer such as breast cancer, ovarian cancer and malignant melanoma, the effect of the raised estrogen level during pregnancy on tumor growth is feared. Thirdly, physiological gestational changes result in 'chemodilution' (reduced blood level of chemotherapy), with a potential impact on drug efficacy.[126,127] Indeed, pregnancy is characterized by an increase in plasma volume of up to 34-70%.[127] In addition, renal blood

flow and glomerular infiltration is increased and hepatic metabolism is altered. Recent human data suggest an increased central distribution volume during pregnancy of 1.19-fold (95% confidence interval (CI) 0.90 – 1.50), 2.27-fold (95% CI 1.57 – 3.10), 1.08-fold (95% CI 0.85 – 1.35) and 1.79-fold (95% CI 1.49 – 2.12) for docetaxel, paclitaxel, doxorubicin and epirubicin, respectively. [128] Clinically this results in a decrease in chemotherapy exposure, variating from 1% (epirubicin) to 13% (paclitaxel) of the area under the plasma concentration-time curve (AUC) in non-pregnant patients.[129] These results do not directly warrant dose adjustments for the studied drugs, however underscore the need to investigate the efficacy of chemotherapy in pregnancy.

Because of the rarity of cases, studies on this topic are mostly retrospective without information on other prognostic factors, resulting in inconsistent results. Large population-based cohort studies showed no increase in cause-specific death in patients with a diagnosis of cancer during pregnancy. Data on 42511 women aged 16 to 49 years, obtained from the cancer registry and the medical Birth registry of Norway, revealed no difference in cause-specific survival for women diagnosed with cancer during pregnancy or lactation, for most cancer types.[8] However, a diagnosis of malignant melanoma during pregnancy slightly increases the risk. Breast and ovarian cancer during lactation did show an increased risk of death. Hence, in the research of maternal prognosis following breast cancer it is important to make a clear distinction between breast cancer diagnosed during pregnancy (BCP) and postpartum breast cancer diagnosis, as this appears to be a distinct entity with a higher aggressive potential.[130]

BCP, the most common cancer type registered in INCIP, usually presents with characteristics of high malignancy and often requires consideration of antenatal chemotherapy.[4,131] Available studies in prognosis following BCP are limited in evidence because of small numbers, and in most studies information on antenatal treatment is not provided.[54,132-135] Interpretation of the available literature is complicated as many cohorts focus on pregnancy-associated breast cancer, also including women with a diagnosis of breast cancer after delivery. In a recent meta-analysis in 2020 data from 45 studies was pooled.[136] There was an overall mortality hazard ratio (HR) of 1.46 95% CI: 1.12-1.90) in fourteen studies that provided separate results for women with breast cancer during pregnancy. Substantial heterogeneity was found in these studies and the most recent and largest studies found no increase in mortality after adjustment for tumor characteristics.[131,135,137,138]

The German Breast Cancer Group (GBG) and INCIP previously joined forces to publish on the largest cohort to date on BCP prognosis.[54,138] In a multicenter cohort study the outcome of 311 pregnant patients with a breast cancer diagnosis was compared to 865 patients with breast cancer that was not associated with a pregnancy. Median follow-up was 61 months. In multivariable cox regression analysis, the observed Hazard Ratio (HR) for disease-free survival (DFS) survival for pregnant patients compared to non-pregnant patients was 1.34, however with the available number of patients the 95% confidence interval was relatively wide (0.93 – 1.91; p=0.14) and the number of patients who received antenatal chemotherapy was insufficiently large to draw firm conclusions.[138]

Hodgkin lymphoma (HL) represents the most common hematological malignancy.[7,24] Management of HL consists of ABVD (doxorubicin, bleomycin, vinblastine, dacarbazine) chemotherapy with or without subsequent radiotherapy.[139,140] Relatively small series evaluating survival in pregnant patients diagnosed with HL show a maternal outcome similar to the non-pregnant population, however do not report on antenatal management in detail. [85,141,142] Large-scale studies are necessary to consolidate these findings.

III. Objectives of the PhD

We aimed to further investigate and build evidence regarding the fetal safety and maternal outcome following cancer treatment during pregnancy. The objectives of this PhD were:

1. To expand and increase the visibility of the INCIP registry in order to enlarge the numbers enabling sub-analyses with regard to obstetrical and neonatal outcome per therapy or tumor type.

   Therefore: a. the web-based INCIP database was improved and was adapted according the updated General Data Protection Regulation (GDPR, 05/2018).

   b. a narrative review was performed (incorporated in the general introduction)

   c. Based on the INCIP database a more in-depth research on risk factors for unfavorable outcomes for both mother and her child was performed (chapter 1). The obstetric and neonatal outcome of all registered cases was correlated by maternal cancer type (chapter 2) and treatment timing or modality (chapter 3, 4 and 5).

2. To further explore the association between chemotherapy and fetal growth and to identify specific treatment regimens and doses that bring the fetus at risk for growth restriction.

By focusing on the occurrence of FGR in pregnancies exposed to chemotherapy this PhD project aims to evaluate if any dose-response effect of chemotherapy on fetal growth exists, or whether there is a specific time window at increased risk in pregnancy, using the INCIP database (chapter 6).

3. To provide more solid evidence on whether antenatal cancer treatment, and its eventual adaptations, affects the prognosis in pregnant patients with breast cancer (chapter 7) and pregnant patients diagnosed with lymphoma (chapter 8). Therefore the INCIP database was analyzed, together with the database of the German Breast Group.

Part II - INCIP REGISTRATION STUDY

Chapter I - Prognostic factors for adverse obstetric outcomes in 2172 pregnant cancer patients in the registry of the International Network on Cancer, Infertility and Pregnancy

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Abstract

The previous report of The International Network on Cancer, Infertility and Pregnancy (INCIP) showed that cancer treatment during pregnancy and aiming for a term delivery, leads to less elective preterm births and less neonatal intensive care unit (NICU) admissions, but more small for gestational age (SGA) neonates. In the present study, we determined in-depth what treatment-, cancer- or patient-specific factors put the future mother and child at risk of obstetric complications. Women with primary or recurrent cancer during pregnancy or women who conceived while receiving invasive cancer treatment between 1996 and 2021 were selected from the INCIP registry (n=2172). Logistic regression models were used to assess evolution of management and outcomes over time, specific factors for adverse obstetric and neonatal outcomes and the association between prognostic factors and SGA. Compared to the general population, preterm delivery (47%), SGA (27%) and NICU admission (33%) are more common in pregnant women with cancer. Most important prognostic factors for adverse obstetric outcomes were antenatal chemotherapy, leukemia and metastatic disease. In multivariable analysis, including stage of disease, smoking and cancer treatment, gestational age at diagnosis remained significantly negatively associated with SGA. These data show that pregnant cancer patients have a high risk of obstetric complications due to multiple risk factors, especially when receiving antenatal chemotherapy.

Introduction

As a result of reassuring reports on obstetric and neonatal outcomes following cytotoxic treatment during pregnancy, a large interim analysis of 1170 pregnant cancer patients by the International Network on Cancer, Infertility and Pregnancy (INCIP) published in 2018, showed that management of pregnant cancer patients had shifted from recommending termination of pregnancy to more often offering oncological treatment during pregnancy.[100] This practice resulted in fewer preterm deliveries, but more small for gestational age (SGA) infants and neonatal intensive care unit (NICU) admissions. Population-based studies have shown an increased risk of adverse obstetric (preterm labor and preterm delivery) and neonatal adverse outcomes (SGA and NICU admission) in pregnant cancer patients, however the exact impact of antenatal cancer treatment is still underinvestigated.[9,11,13,17,143,144] Small cohort studies focusing specifically on chemotherapy-exposed pregnancies revealed a direct negative effect of chemotherapy exposure on neonatal birthweight, but also suggested that other influencing factors might play a role, such as maternal weight, smoking, hypertension, cancer type and stage of disease.[98,145] Since the last INCIP interim-analysis in 2018, the number of patients in the database has almost doubled. In this updated analysis, we focus in-depth on patient-specific, cancer-specific and treatment-specific factors that influence obstetric and neonatal outcomes in the pregnant cancer population.

Methods

The INCIP registry is an international observational cohort study (ClinicalTrials.gov (NCT00330447)). This report includes all registered pregnant women with primary or recurrent cancer or women who conceived while receiving cancer treatment between January 1996 and June 2021.

The assessed patient-specific, cancer-specific, and treatment-specific factors include maternal weight gain ,cancer type, cancer stage (local versus metastatic disease), primary or recurrent disease and treatment regimen. Stage of oncological disease was stratified as local disease (TNM or FIGO stage I-III cancers, as well as brain tumors), metastatic disease (TNM or FIGO stage IV) and leukemia (and other myeloproliferative disease). Primary outcomes were preterm spontaneous labor (Preterm Premature Rupture of Membranes (PPROM) and/or preterm contractions), (elective or spontaneous) preterm delivery, SGA, NICU admission, pregnancy loss (miscarriages and stillbirths), maternal death and cesarean section. Secondarily, we were interested in reported obstetric complications (such as venous thromboembolism (VTE), pre-eclampsia and infection). SGA was defined as a birthweight percentile below 10, assessed according to the customized calculator of Gestation Network.[146] Maternal weight gain was expressed according to the reference range in a low risk pregnant population.[147] Chemotherapy duration was defined as the interval between the first exposure and the last exposure during pregnancy, adding the duration of one chemotherapy cycle or the duration from last exposure to birth if the patient delivered earlier. Comparable to the previous INCIP analysis,

the cohort was divided into four subgroups according to year of diagnosis: 1996-2004; 2005-2009; 2010-2015, and 2016-2021.[53,100] Hence, cases with a primary cancer diagnosis in pregnancy diagnosed between 1996-2016 are overlapping with previous INCIP analysis, whereas all cancer recurrences from 1996-2016 and cases retro- or prospectively registered since November 2016 are newly reported.[100]

Statistical analysis

Descriptive statistics were used to present oncological and obstetric data. Obstetric and neonatal outcomes were compared to the expected rates in the general population, based on international references as reported[148-156], using binomial test for a single proportion.

Obstetric and neonatal outcomes, and complications of pregnant women that received antenatal chemotherapy were compared to pregnant women that did not receive chemotherapy, using the Chi Square test or Fisher exact test, as appropriate. For this analysis we focused on ongoing singleton pregnancies (>20 weeks of gestation), excluding twin pregnancies, miscarriages and pregnancy terminations prior to 20 weeks of gestation.

For the assessment of the evolution of oncological management and obstetric outcome over 25 years, we used log-binomial regression models with year of diagnosis as a continuous predictor. We express results using relative risks (RR) with 95% confidence intervals to describe differences between time periods or a global trend over time.

Logistic regression model were used to explore the relationship between patient-specific, cancer-specific and treatment-specific predictors (maternal age at cancer diagnosis, cancer type, treatment modality, cancer stage at diagnosis) and obstetric outcome [(preterm spontaneous labor, (planned or spontaneous) preterm delivery, SGA, admission in the NICU, pregnancy loss (miscarriages and still births, excluding all pregnancy terminations), cesarean section and maternal death]. For maternal death we included all available cases. For pregnancy loss, we assessed al spontaneous miscarriages and stillbirths; terminations of pregnancy were excluded. All singleton ongoing pregnancies (>20 weeks of gestation) were used for analyses of obstetric outcomes. We focused on singleton live births only when assessing SGA, neonatal complications and NICU admission. As previous studies showed a significant impact of antenatal chemotherapy on obstetric outcomes, this was included as a confounder factor in the model. The analysis for chemotherapy regimens was corrected for cancer subtype, as in exploratory analysis these predictors were highly related.

Potential predictors for SGA (cancer type, antenatal treatment modality, maternal weight, diabetes, hypertension, smoking, substance) in univariable logistic regression analysis ($p<0.2$) were included in a multivariable model. As interval between diagnosis and delivery and gestational age at diagnosis are highly related, these confounders could not be included in the same multivariable linear regression model. We opted to explore the effect of gestational age at diagnosis, as this is a rather fixed factor.

In addition, we explored the effect of chemotherapy duration on neonatal birthweight in a subgroup analysis of women receiving chemotherapy during pregnancy. To investigate the impact of taxanes, as an additional prognostic factor, on neonatal birthweight we performed a subgroup analysis in all pregnant breast cancer patients who received chemotherapy (doxorubicin-cyclophosphamide (AC)/ epirubicin-cyclophosphamide(EC)/ 5-FU-doxorubicin-cyclophosphamide (FAC)/ 5-FU-epirubicin-cyclophosphamide FEC with or without taxanes). To explore the effect of chemo dosages on neonatal birthweight we performed a subgroup analysis in all pregnant breast cancer patients who received only anthracycline-based treatment (AC/EC, without taxanes).

For the regression models, missing values in both outcomes and predictor variables were dealt with by means of multiple imputation. Ten imputation data sets were constructed by fully conditional specification (FCS). Analyses were performed on each completed data set and combined into unique summary statistics accounting for uncertainty due to the imputations. Multiple imputation was not used for the log-binomial regression models to assess the evolution of management and obstetric outcome over time. All tests are two-sided and evaluated at a 5% significance level. Analyses have been performed using SPSS (version 28.0) and SAS software (version 9.4 of the SAS System for Windows).

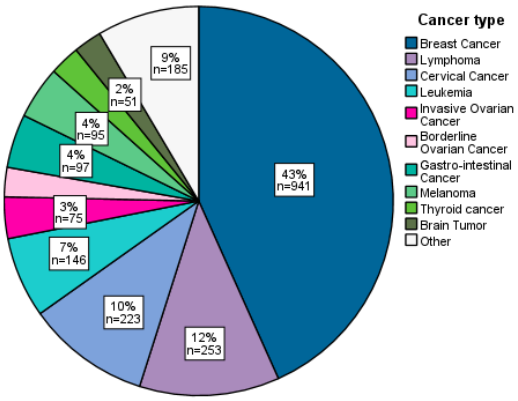
Results

Patient characteristics

In total, 2172 eligible pregnant women, mostly registered in Belgium (22%), the Netherlands (21%), the United States of America (16%), Italy (13%) and Russia (9%), were selected from the registry (Table 1, see study flow chart Figure SII-I.1). The most common cancer types were breast cancer (43%), followed by lymphoma (12%), cervical cancer (10%) and leukemia (7%) (Figure 1, see Table SII-I.1 for specification of 'other cancers'). Patients were most frequently diagnosed with cancer between 13 and 24 weeks of gestation (35%). Metastatic disease was present in 12%. A minority of pregnant women was diagnosed with recurrent cancer (5%), mostly breast cancer (25%), melanoma (18%) and borderline ovarian tumors (10%) (see Figure SII-I.3 and 4, Table SII-I.4). In 58 women (3%) pregnancy was detected during cancer treatment. Most patients received chemotherapy during pregnancy (25%), surgery (19%), or a combination of cancer treatments (23%). See Figure SII-I.5 and Table SII-I.5 and I.6 for descriptive statistics per cancer type.

Figure 1: Distribution of cancer types and cancer stages at diagnosis by cancer type (n=2172).

Other cancers include (in order of frequency): myeloproliferative neoplasias, renal cancer, lung cancer, sarcoma, basal cell carcinoma, bladder cancer, nasopharyngeal tumor, vulvar cancer, choriocarcinoma, oral cavity tumor, vaginal cancer, multiple myeloma, adrenal gland tumor, endometrial cancer, salivary gland tumor, laryngeal tumor, myelodysplastic syndromes.



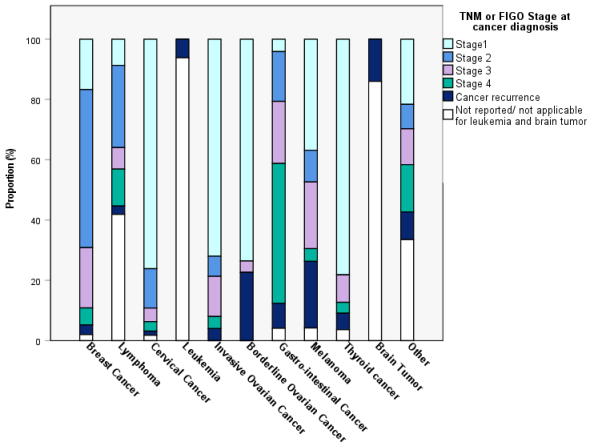


Table 1: Patient characteristics (n=2172)

Characteristic	Median (IQR; range)	N.	%
Age at diagnosis			
Median (IQR; range)	33(7; 14-53)		
Missing data		57	
Period at diagnosis			
1996-2004		358	16.5
2005-2009		489	22.5
2010-2015		742	34.2
2016-2021		583	26.8
Timing of diagnosis			
Median GA at diagnosis (IQR, range)	19.3 (14.7; 0-41.4)		
Diagnosis before pregnancy		129	6.1
<13 weeks of gestation		546	25.7
13-23 weeks of gestation		749	35.2
24-32 weeks of gestation		450	21.2
>32 weeks		251	11.8
Missing data		47	
Oncological diagnosis			
Breast cancer		941	43.3
Lymphoma		253	11.6
Cervical cancer		223	10.3
Leukemia		146	6.7
Invasive ovarian cancer		75	3.5
Borderline ovarian tumors		53	2.4
Gastro-intestinal cancer		97	4.5
Melanoma		95	4.4
Thyroid cancer		55	2.5
Brain tumor		51	2.3
Other		185	8.5
Stage of disease			
Local or regional		1542	80.8
Systemic disease		367	19.2
Metastatic disease		221	11.6
Leukemia		146	7.6
Missing data		263	
Recurrent cancer diagnosed during pregnancy		120	5.5
Maternal BMI			
Median (IQR, range)	23.9 (5.6; 13.5-59.5)		
Missing data		825	
Maternal Weight evolution during pregnancy[a]			
Median (IQR, range), in percentiles*	13 (36; 0-100)		
<10th percentile		235	44.3
10-50th percentile		192	36.3
51-90 percentile		89	16.8
>90 percentile		14	2.6
Missing data		1642	

Treatment during pregnancy				
No treatment/cancer surveillance		177		8.1
Planned delivery to initiate treatment		298		13.7
Termination of pregnancy		167		7.7
Surgery		401		18.5
Chemotherapy		540		24.9
Radiotherapy		11		0.5
Targeted or immunomodulatory therapy[b]		83		3.8
Hormonal treatment		3		0.1
Treatment combinations		492		22.7
Surgery and chemotherapy		392		18.0
Surgery and radiotherapy		17		0.8
Surgery, chemotherapy and radiotherapy		15		0.7
Chemotherapy and radiotherapy		5		0.2
Other treatment combinations		63		2.9
Pregnancy outcome				
Live birth		1931		88.9
Singleton			1887	97.7
Twin			43	2.2
Triplet			1	0.1
Miscarriage		46		2.1
Termination of pregnancy		167		7.7
Stillbirth		27		1.3
Molar pregnancy		1		0
Birthweight, in gram*	2760 (858; 354-6000)			
Birthweight, in percentile*				
<P10		434		26.7
P10-P24		368		22.6
P25-P49		359		221
P50-P74		189		11.7
P75-P90		158		9.7
>P90		118		7.3
Missing data		260		
Interval diagnosis and delivery (weeks)				
Median (IQR, range)	14.4 (18.4; 0-42.1)			
Missing data		61		
Smoking				
Smoking in pregnancy		69		5.6
No smoking in pregnancy		1156		94.4
Missing data		947		
Substance				
Substance use in pregnancy		24		2.1
No substance use		1144		97.9
Missing data		1004		

Percentages are based on total number of known data.
[a]reference: Santos et al.
[b]mainly includes rituximab and interferon
* singleton live births only excludes still births, (n=1886)

Obstetric and neonatal outcomes

Of the 1934 ongoing singleton pregnancies (>20 weeks of gestation), there were 97% live births, 2% stillbirths and 1% pregnancy terminations, mostly for oncological reasons (83%). Compared to the general population, preterm delivery (47%) and delivery by cesarean section (46%) are more common in pregnant cancer patients.[157,158] Neonatal outcomes are more often complicated by SGA (27%) and NICU admission (33%).[152,159] Most obstetric complications (maternal infection, venous thromboembolism (VTE)) were more frequently reported in women who received antenatal chemotherapy compared to women who did not (Table 2, see Table SII-I.2 for more details).

Table 2: Obstetric outcomes and complications of ongoing singleton pregnancies (>20 weeks of gestation) by receipt of antenatal chemotherapy (n=1934)

Obstetric outcomes	Missing	Total		% general population[(ref)], p value[Δ]	Antenatal chemotherapy (n=990)		No antenatal chemotherapy (n=944)		p-value
		N.	%		N.	%	No	%	
Obstetrical complications									
Preterm spontaneous labor	66	236/1868	12.6	5%[(a)], p<0.001	173/975	17.7	63/893	7.1	<0.001
With preterm birth		215/1868	11.5		160/975	16.4	55/893	6.2	<0.001
With term birth		21/1868	1.1		13/975	1.3	8/893	0.9	0.390
PET/HELLP	405	54/1529	3.5	°	26/693	3.8	28/836	3.3	0.679
GDM	405	97/1529	6.3	°	47/693	6.7	50/836	6.0	0.529
APH[1]	405	22/1529	1.4	°	12/693	1.7	10/836	1.2	0.397
Cholestasis	405	14/1529	0.9	°	8/693	1.2	6/836	0.7	0.426
PIH	405	19/1529	1.2	°	8/693	1.2	11/836	1.3	0.821
Chorio-amnionitis	405	7/1529	0.5	°	6/693	0.9	1/836	0.1	0.051
Medical complications	405								
Maternal infection		60/1529	3.9	°	38/693	5.5	22/836	2.6	0.005
Hematological[2]		30/1529	2.0	°	25/693	3.6	5/836	0.6	<0.001
VTE		18/1529	1.2	°	14/693	2.0	4/836	0.5	0.007
Low maternal weight gain[Δ]	1418	234/516	45.4	10%[(b)], p<0.001	165/325	50.7	69/191	36.2	0.001
Major congenital malformations	218	47/1716	2.7	3%[(c)], p=0.381	30/919	2.0	17/798	2.1	0.182
Preterm delivery*	89	859/1824	47.1	8%[(d)], p<0.001	500/964	51.8	359/860	41.7	<0.001
20-24 weeks	89	11/1824	0.6	Early preterm	4/965	0.4	7/859	0.8	0.367
24-28 weeks		23/1824	1.3	(<34): 2%[(d)],	12/965	1.2	11/859	1.3	1
28-32 weeks		96/1824	5.3	p<0.001	46/965	4.8	50/859	5.8	0.345
32-34 weeks		166/1824	9.1	Late preterm	88/965	9.1	78/859	9.1	1
34-36 weeks		561/1824	30.8	(34-36w): 6%[(d)],	349/965	36.2	212/859	24.7	<0.001
>=37 weeks		967/1824	53.0	p<0.001	466/965	48.3	501/859	58.3	<0.001
Elective preterm delivery*	106	675/1807	37.4		367/959	38.3	308/848	36.3	0.408
Spontaneous preterm delivery*	106	169/1807	9.4		128/959	13.3	41/848	4.8	<0.001
Onset of labor*	30								
Spontaneous		618/1883	32.8	47%[(d)], p<0.001	308/977	31.5	310/906	34.2	0.220
Induction of labor		567/1883	30.1	34%[(d)], p<0.001	332/977	34.0	235/906	25.9	<0.001
No labor (primary CS)		698/1883	37.1	18%[(d)], p<0.001	337/977	34.5	361/906	39.8	0.017
Mode of delivery**									
Delivery by CS	46	843/1840	45.8	26%[(e)],p<0.001	427/959	44.5	416/881	47.1	0.261
Vaginal delivery	46	997/1840	54.1		532/959	55.4	465/881	52.8	0.261
PPH**	400	10/1486	0.65	°	9/683	1.3	1/803	0.1	0.007
SGA**	260	434/1626	27.0	10%[(f)], p<0.001	283/908	31.2	151/718	21.0	<0.001
NICU admission**	291	531/1595	33.2	7.8%[(g)], p<0.001	289/836	34.5	242/759	31.9	0.264
Preterm (<37w)		452/1595	28.3		247/836	29.5	205/759	27.0	0.266
Term (≥37w)		79/1595	5.0		42/836	5.0	37/759	3.9	0.909
Neonatal complications[**,3]**									
Infection	179	48/1707	2.8	°	31/911	3.4	17/796	2.11	0.142
Hematological	179	22/1707	1.3	°	13/911	1.4	9/796	1.1	0.670
Respiratory	179	79/1707	4.6	°	40/911	4.4	39/796	4.9	0.645
Neonatal death**	180	8/1706	0.5	0.1%[(h)], p<0.001	4/910	0.4	4/796	0.5	1.000

Abbreviations: PET: pre-eclampsia; HELLP: Hemolysis Elevated Liver enzymes and Low Platelets; GDM: Gestational Diabetes Mellitus; APH: Antepartum hemorrhage; PIH: Pregnancy-Induced Hypertension; PPH: Postpartum Hemorrhage; VTE: Venous Thromboembolism; CS: Cesarean section; SGA: Small for Gestational Age; NICU: Neonatal Intensive Care Unit

Preterm spontaneous labor includes PPROM (Preterm premature rupture of membranes) and preterm contractions

* singleton live and still births, excludes 21 cases of pregnancy termination between 20-24 weeks of gestation (n=1913)

** singleton live births only excludes still births, (n=1886)

[1] Placental abruption or vaginal bleeding after 20 weeks of gestation

[2] **Hematological medical complications** include severe anemia, neutropenia or thrombocytopenia requiring hospitalization (with correction) or a delay of treatment

[3] **Neonatal infectious complications** include systemic infection, sepsis, necrotizing enterocolitis (NEC). **Neonatal hematological complications** include all cases with reported anemia, neutropenia, thrombocytopenia and severe neonatal icterus. **Neonatal respiratory complications** include Infant respiratory distress syndrome (IRDS) requiring intubation, pneumothorax, respiratory distress with re-animation and severe asphyxia.

[Δ] Low weight gain was defined as a maternal weight evolution below the 10th percentile (Santos et al).

References: a: Preterm labor and birth, NICE guideline Published: 20 November 2015 www.nice.org.uk/guidance/ng25; b: Santos S, Eekhout I, Voerman E, et al. Gestational weight gain charts for different body mass index groups for women in Europe, North America, and Oceania. BMC Med 2018;16:201; c: https://eu-rd-platform.jrc.ec.europa.eu/eurocat/eurocat-data/prevalence_en; accessed 25-03-2022; d: Health and Social Care Information Centre https://digital.nhs.uk/data-and-information/publications/statistical/nhs-maternity-statistics/2020-21; e: Health and Social Care Information Centre. NHS Maternity Statistics - England, April 2012 to March 2013: Provider level analysis. [Leeds]: HSCIC; 2013 [http://www.hscic. gov.uk/catalogue/PUB12744].f: based on the definition of SGA; g: Wade Harrison, MPH1; David Goodman, MD, MS1. Epidemiologic Trends in Neonatal Intensive Care, 2007-2012. JAMA Pediatr. 2015;169(9):855-862. doi:10.1001/jamapediatrics.2015.1305; h: WHO (high-income countries) https://www.who.int/news-room/fact-sheets/detail/levels-and-trends-in-child-mortality-report-2021

°reported percentages are not compared to the general population as they might be under- or misreported in the INCIP database. Population-based studies are better tools to address these incidences.

Table 3: Prognostic factors for most common obstetric complications by logistic regression analysis

	Preterm spontaneous labor		Preterm delivery <37weeks		Spontaneous preterm delivery <37 weeks		SGA		NICU admission	
	OR(95% CI)	p	OR(95% CI)	p	OR(95% CI)	p	OR(95% CI)	p	OR(95% CI)	p
Cancer type										
Breast cancer=ref.		<0.01		<0.01		0.01		0.01		<0.01
Borderline OvTumor	0.24(0.03;1.79)		0.09 (0.03;0.29)		0.31 (0.04;2.34)		0.50 (0.19;1.31)		0.24 (0.07;0.78)	
Brain Tumor	0.76(0.23;2.54)		1.18 (0.64;2.18)		0.80 (0.19;3.46)		1.06 (0.46;2.45)		2.23 (1.15;4.31)	
Cervical Cancer	0.76(0.44;1.33)		1.97 (1.41;2.75)		0.67 (0.33;1.34)		1.14 (0.77;1.69)		2.37 (1.67;3.37)	
Gastro-intestinal	0.43(0.15;1.20)		3.15 (1.87;5.31)		0.38 (0.10;1.53)		1.32 (0.74;2.36)		5.05 (3.01;8.49)	
Leukemia	2.75(1.73;4.37)		1.60 (1.09;2.35)		2.55 (1.53;4.27)		1.95 (1.27;3.02)		3.00 (2.00;4.50)	
Lymphoma	1.70(1.17;2.48)		1.09 (0.81;1.46)		1.44 (0.94;2.21)		1.34 (0.95;1.89)		1.11 (0.78;1.57)	
Melanoma	0.74(0.28;1.94)		0.40 (0.23;0.68)		0.44 (0.10;1.94)		0.93 (0.48;1.80)		0.69 (0.36;1.31)	
Other cancer	0.53 (0.2;1.18)		1.05 (0.72;1.54)		0.88 (0.40;1.92)		1.91 (1.12;3.26)		1.85 (1.11;3.09)	
Ovarian Cancer	0.63 (0.25;1.61)		1.0 (0.60;1.66)		0.05(0.0;14E12)		1.25 (0.69;2.26)		1.15 (0.62;2.14)	
Thyroid cancer	0.25 (0.03;1.87)		0.09 (0.01;0.25)		0.32 (0.04;2.44)		0.48 (0.16;1.42)		0.23 (0.07;0.72)	
Period of diagnosis										
1996-2004= ref.		0.78		<0.01		0.14		0.26		<0.01
2005-2009	1.18 (0.72;1.96)		0.85 (0.62;1.15)		0.98 (0.53;1.79)		0.92 (0.64;1.32)		0.82 (0.50;1.14)	
2010-2015	1.19 (0.75;1.89)		0.65 (0.49;0.86)		1.22 (0.69;2.13)		1.03 (0.73;1.45)		0.65 (0.49;0.88)	
2016-2021	1.28 (0.80;2.05)		0.59 (0.44;0.79)		1.58 (0.92;2.74)		1.24 (0.88;1.74)		0.55 (0.40;0.75)	
Period of diagnosis										
1996-2004	0.83 (0.53;1.32)	0.78	1.54 (1.16;2.05)	<0.01	0.82 (0.47;1.44)	0.14	0.97 (0.80;1.37)	0.26	1.53 (1.14;2.06)	<0.01
2005-2009	0.99 (0.68;1.46)		1.31 (1.02;1.69)		0.80 (0.50;1.28)		0.89 (0.66;1.22)		1.26 (0.97;1.65)	
2010-2015= ref.										
2016-2021	1.07 (0.77;1.51)		0.90 (0.71;1.14)		1.30 (0.90;1.90)		1.21 (0.92;1.58)		0.84 (0.64;1.09)	
Systemic Disease										
Local = ref.		<0.01		<0.01		0.01		<0.01		<0.01
Metastatic	1.18 (0.73;1.92)		2.39 (1.74;3.27)		1.17 (0.65;2.09)		1.68 (1.18;2.39)		2.74 (1.99;3.76)	
Leukemia	2.36 (1.53;3.65)		1.40 (1.00;1.96)		2.26 (1.39;3.68)		2.40 (1.56;3.68)		2.28 (1.52;3.40)	
Recurrent disease (yes vs no)	1.69 (0.92;3.09)	0.089	1.08 (0.71;1.63)	0.73	0.90 (0.38;2.13)	0.81	1.25 (0.75;2.09)	0.39	1.40 (0.90;2.20)	0.14
Chemotherapy (yes vs no)	2.89(2.13;3.91)	<0.01	1.55 (1.28;1.86)	<0.01	2.71 (1.82;4.04)	<0.01	1.71 (1.36;2.13)	<0.01	1.17 (0.96;1.43)	0.55
Anthracyclines	2.60 (1.82;3.72)	<0.01	1.23 (0.98;1.55)	<0.01	2.49 (1.62;3.83)	<0.01	1.14 (0.85;1.52)	0.38	1.04 (0.79;1.37)	0.79
Alkylating agents	2.48 (1.76;3.50)	<0.01	1.01 (0.80;1.27)	0.94	2.24 (1.51;3.32)	<0.01	1.22 (0.92;1.62)	0.16	0.91 (0.70;1.20)	0.50
Taxanes	1.53 (1.02;2.31)	0.04	1.22 (0.91;1.63)	0.18	1.50 (0.94;2.40)	0.09	2.10 (1.52;2.89)	<0.01	1.55 (1.12;2.17)	<0.01
Platinum agents	2.11 (1.09;4.10)	0.03	3.52 (2.33;5.34)	<0.01	1.84 (0.81;4.17)	0.14	2.72 (1.74;4.24)	<0.01	3.06 (1.99;4.40)	<0.01
Antimetabolites	1.11 (0.70;1.75)	0.67	1.17 (0.85;1.61)	0.34	1.00 (0.60;1.70)	1.00	1.65 (1.16;2.35)	0.01	1.57 (1.13;2.20)	0.01
Other*	1.99 (1.28;3.09)	<0.01	0.96 (0.68;1.36)	0.82	1.64 (1.00;2.71)	0.06	1.20 (0.81;1.77)	0.37	0.89 (0.6;1.30)	0.53
Surgery during pregnancy (yes vs no)	0.83 (0.63;1.11)	0.21	0.67 (0.55;0.81)	<0.01	0.86 (0.61;1.20)	0.38	0.87 (0.69;1.09)	0.23	0.61 (0.49;0.75)	<0.01
Type of surgery**										
Extra-abd surg =ref.		0.57		0.29		0.10		0.63		0.68
Abdominal surg	0.69 (0.34;1.38)		0.74 (0.49;1.12)		0.35 (0.13;0.91)		1.26 (0.80;1.99)		0.96 (0.60;1.53)	
Uterine surg	0.86 (0.20;3.82)		0.72 (0.30;1.69)		-		0.87 (0.25;3.02)		0.61 (0.20;1.85)	
Radiotherapy (yes vs no)	0.80 (0.31;2.05)	0.64	1.20 (0.70;2.10)	0.51	1.37 (0.57;3.29)	0.489	1.63 (0.85;3.16)	0.14	1.16 (0.62;2.18)	0.64
Target or immunomodulatory therapy (yes vs no)	2.15 (1.34;3.45)	<0.01	0.99 (0.67;1.46)	0.97	1.97 (1.16;3.36)	0.013	1.87 (1.16;3.03)	0.01	1.44 (0.85;2.41)	0.17
Age at diagnosis (per 5 years)	0.79 (0.70;0.90)	<0.01	0.94 (0.86;1.02)	0.12	0.81 (0.70;0.94)	0.05	0.90 (0.81;1.00)	0.05	0.90 (0.81;1.00)	0.04
Low weight gain (yes vs no)	1.06 (0.62;1.82)	0.81	1.12 (0.75;1.70)	0.54	1.05 (0.53;2.06)	0.89	1.48 (0.90;2.46)	0.12	1.25 (0.85;1.83)	0.24

Abbreviations: Surg: sugery, OvTumor: Ovarian Tumor; Extra-abd: extra-abdominal

For all predictors, except antenatal chemotherapy, analysis were corrected for the receipt of antenatal chemotherapy. For chemotherapy regimens during pregnancy, analyses were corrected for cancer type (4 cat: breast cancer, gynecological cancer, hematological and other)

For preterm spontaneous labor and other obstetric complications: singleton ongoing pregnancies (n=1935). For preterm delivery: singleton live births and still births (n=1914). For SGA and NICU (neonatal outcome): singleton live births only(n=1886)

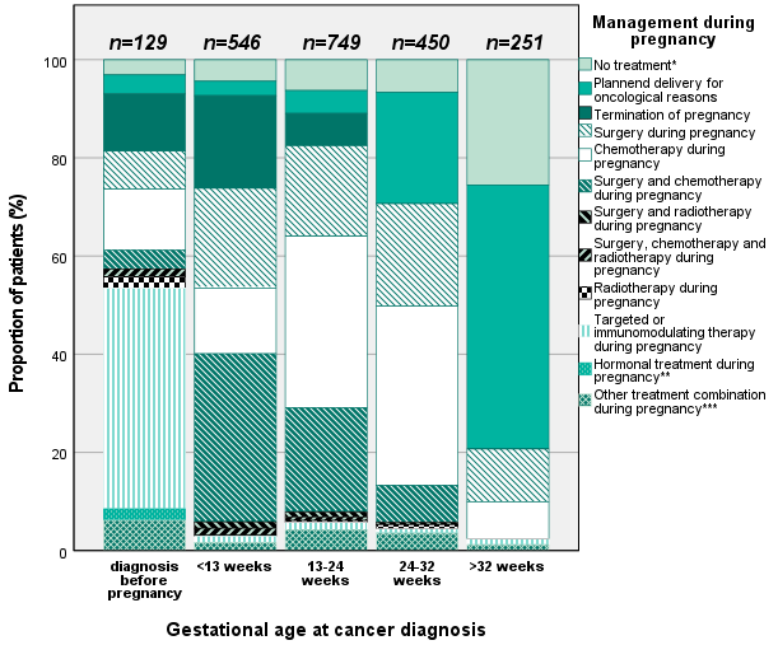
* Other chemotherapy types (in order of frequency): Vinca alkaloids, Bleomycin, Etoposide, ATRA, L-asparaginase, Methotrexate, Temozolomide, Irinotecan, Actinomycin

** Only cases with surgery during pregnancy included (n total=845)

A diagnosis of lymphoma, leukemia and the administration of antenatal chemotherapy (all chemotherapy regimens, except antimetabolites) appeared to be risk factors for preterm spontaneous labor (Table 3, see Table SII-I.7 and 8). Elective preterm delivery was more often observed in women with cervical cancer or gastro-intestinal cancer, whereas for women with leukemia there was an increased risk of spontaneous preterm delivery. Risk factors for SGA were a diagnosis of leukemia, metastatic disease, the administration of antenatal chemotherapy (greatest impact for platinum agents and taxanes) and targeted or immunomodulatory therapy. NICU admission, which was mostly related to prematurity (85%), was dependent

of cancer type, occurring more frequently for neonates of mothers with gastro-intestinal cancers, leukemia, cervical cancers, and brain tumors, as well as in metastatic disease. For thyroid cancers and borderline ovarian tumors the risk was the lowest. Also the receipt of platinum agents, taxanes and antimetabolites increased the risk of NICU admission. Metastatic disease was a risk factor for both pregnancy loss and maternal death. Maternal death occurred most often in pregnant women diagnosed with gastro-intestinal cancers, leukemia, brain tumors and melanoma.

Figure 2: Management of primary or recurrent cancer related to timing of diagnosis (n=2125[Δ])



[Δ] Excluding 47 cases where exact gestational age at diagnosis was not reported
**Include 4 women with cancer diagnosis prior to pregnancy: 1 women with Precursor B-cell lymphoblastic leukemia who experienced an early miscarriage; 1 women with astrocytoma of the brain who experienced a still birth; 1 women who became pregnant following endoscopic resection of early stage gastric cancer and delivered term; 1 women with metastatic breast cancer who refused treatment and experienced an early miscarriage.*
***In all 7 women who received hormonal treatment (3 in monotherapy, 4 in combination therapy) pregnancy was detected while treated for breast cancer.*
**** Other Treatment combinations include (in order of frequency): chemotherapy and radiotherapy; chemotherapy, hormonal therapy and radiotherapy; surgery and target therapy; surgery, chemotherapy and target therapy; chemotherapy, target therapy and radiotherapy; chemotherapy and hormonal therapy.*

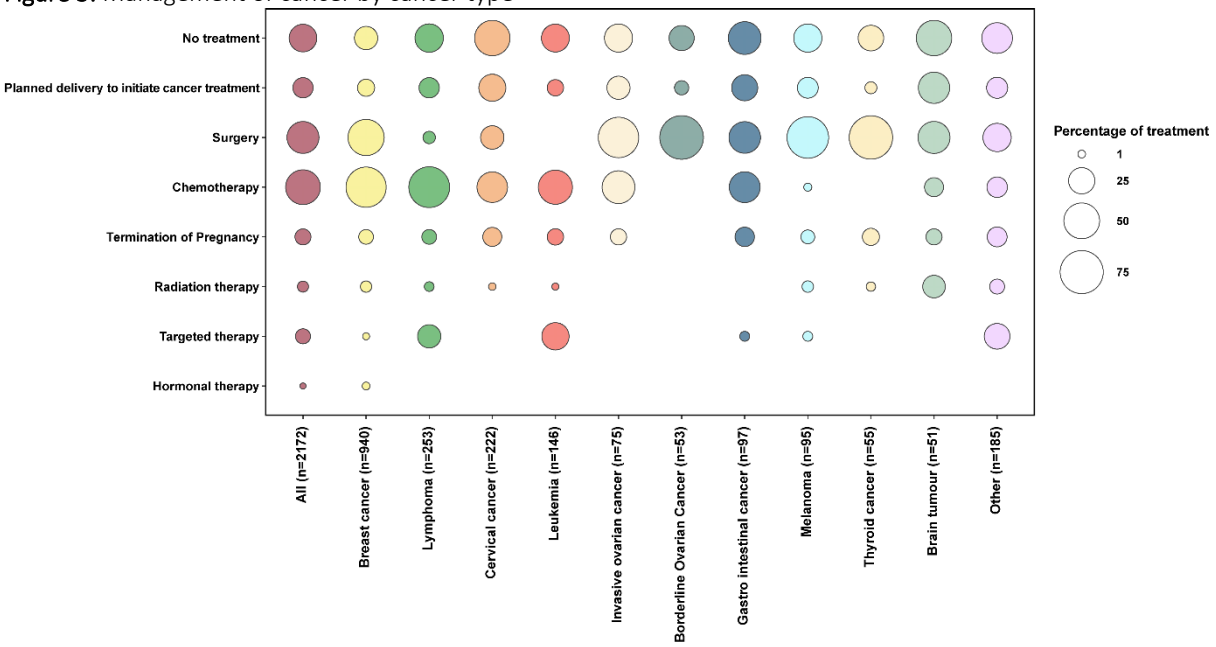
<u>Changes in oncological management and obstetric outcomes over time</u>

Figure 2 and figure 3 provide an overview of management related to timing of diagnosis and cancer type, respectively. Besides a decrease in surgery during pregnancy (RR 0.78 95%CI[0.67-0.90], p<0.001), overall management (including antenatal chemotherapy) of cancer in pregnancy, pregnancy outcomes and incidence of preterm delivery did not significantly change in the last 5 years, compared to the previous cohort 2010-2016 (see Table SII-I.9). However, over time there were more spontaneous preterm livebirths (mostly between 34-37 weeks), whereas the number of elective preterm livebirths further decreased. Over the period of inclusion (1996-2021), there were less NICU admissions (RR for 1-year increase 0.97 [0.97;0.99], p<0.001) and more SGA infants (RR 1.02[1.00;1.03], p=0.018), however the last 5 years there were no further significant changes. Cesarean section rate remained stable at 44%, for mostly oncological reasons (59%, mainly for cervical cancer and maternal medical deterioration) (see Table SII-I.3).

Over time (1996-2021), there were more patients receiving chemotherapy during pregnancy (RR for 1-year increase 1.19 [1.14:1.24], p<0.001) and more livebirths (RR 1.02 [1.01:1.04], p=0.002), whereas there was a

decrease in patients receiving no treatment in pregnancy (RR 0.87 (0.82:0.93), p<0.001) and pregnancy terminations (RR 0.80 [0.70:0.92], p=0.001) (See Figure SII-I.2 and Table SII-I.9).

Figure 3: Management of cancer by cancer type



Prognostic factors for SGA

In univariable analysis, SGA was significantly negatively associated with time between diagnosis and delivery, metastatic disease, hypertension, cancer type (hematological cancers), smoking, antenatal chemotherapy and targeted or immunomodulatory therapy (Table 4). Expectant oncologic management and a higher gestational age at cancer diagnosis were both significantly associated with a higher birthweight. In multivariable analysis, an early gestational age at diagnosis remained significantly associated with SGA (0.98, 95%CI[0.97;0.99], p=0.039) (Table 4) and low birthweight percentiles (0.25 [0.07;0.44], p=0.01) (see Table SII-I.10).

In the chemotherapy subgroup analysis (see Table SII-I.11-17), the duration of chemotherapy was negatively associated with neonatal birthweight (reduction of birthweight percentile with -0.89 [-1.27;-0.51], p<0.001 by every additional week of chemotherapy), when adjusted for low maternal weight gain, stage of disease, hypertension, targeted therapy and chemotherapy regimens (see Table II-I.14). The dosage of anthracyclines in 308 breast cancer patients treated with AC/EC in pregnancy was negatively correlated with eventual neonatal birthweight percentiles [-0.07 [-0.13;-0.00], p=0.038] (see Table SII-I.17). The addition of taxanes to anthracycline-based treatment in breast cancer patients did not impact neonatal birthweight (see Table SII-I.16).

Table 4: Association between clinical predictors and SGA for all singleton live births (n=1886), assessed by univariable and multivariable regression models

	Univariable models			Multivariable model		
	Estimate	95%CI	p-value	Estimate	95%CI	p-value
GA diagnosis	0.979	0.967;0.991	0.0007	**0.985**	**0.971;0.999**	**0.0390**
Interval diagnosis delivery	1.003	1.001;1.004	0.0006			
Maternal age (years)	0.982	0.962;1.002	0.0843	0.995	0.972;1.019	0.7042
Pre-pregnancy maternal BMI (kg/m2)	1.017	0.989;1.045	0.2256			
Adjusted gestational weight gain (percentile)*	0.991	0.981;1.001	0.0711	0.993	0.983;1.003	0.1577
Stage of disease			0.0001			0.0131
Local disease (=ref)						
Metastatic disease	1.632	1.155;2.306		1.814	1.073;3.066	
Leukemia	2.128	1.389;3.260		1.560	1.065;2.284	
Hypertensive disorder/HELLP/PE	1.779	1.049;3.019	0.0330	1.381	0.711;2.684	0.3392
Diabetes	1.517	0.962;2.393	0.0727	1.189	0.681;2.075	0.5415
Cancer type			0.0005			0.7395
Breast Cancer (ref.)						
Gynaecological Cancer	0.869	0.629;1.201		1.112	0.767;1.612	
Hematological Cancer	1.583	1.173;2.135		1.206	0.755;1.927	
Other	0.793	0.565;1.113		0.933	0.608;1.431	
No antenatal treatment	0.660	0.499;0.871	0.0034	1.141	0.708;1.840	0.5861
Antenatal chemotherapy	1.705	1.362;2.133	<.0001	1.688	1.145;2.490	0.0085
Antenatal surgery	0.858	0.683;1.079	0.1899			
Antenatal radiotherapy	1.553	0.809;2.981	0.1847	1.438	0.722;2.865	0.3005
Antenatal target therapy	1.742	1.080;2.809	0.0235	1.084	0.622;1.890	0.7742
Smoking	1.987	1.103;3.579	0.0236	2.414	1.268;4.596	0.0090
Substance	1.382	0.636;3.001	0.4106			

Abbreviations: GA: Gestational age, BMI: Body mass index, HELLP: Hemolysis Elevated liver enzymes and low platelets; PE: pre-eclampsia

CI: confidence interval

Continuous predictors: Estimate>(<)0: higher (lower) birth weight for higer predictor level

Binary predictors: Estimate>(<)0: higher (lower) birth weight for indicated category compared to reference

Discussion

This study shows that the prevalence of adverse obstetric and neonatal outcomes in pregnant cancer patients is higher than in the general population, and even higher in pregnant women receiving chemotherapy. Risk factors for preterm spontaneous labor and SGA include leukemia and metastatic disease. Early gestational age at cancer diagnosis is also independently associated with SGA. A dose-response effect of chemotherapy is suggested, with lower neonatal birthweight percentiles with increasing chemotherapy duration. Over the last 5 years, the incidence of antenatal chemotherapy, overall preterm birth, NICU admissions and SGA has stabilized. The practice to strive for a term delivery results in fewer elective, however more spontaneous preterm (mostly between 34 and 37 weeks) deliveries.

Antenatal cancer treatment often enables continuation of pregnancy, without compromising maternal prognosis.[160,161] However, this comes at a cost as this cohort shows that exposure to chemotherapy in utero increases the risk of preterm onset of labor, spontaneous preterm delivery and SGA. The larger number of patients in the current analysis compared to our previous paper, allowed us to better explore the effect of different treatment regimens. In line with our hypothesis, both platinum agents and taxanes significantly increased the risk of spontaneous preterm labor, SGA and NICU admission. The rate of elective preterm delivery was not affected by the exposure to antenatal chemotherapy. In this cohort, low maternal weight gain, metastatic disease, leukemia, smoking and gestational age at cancer diagnosis also influenced the birthweight in uni- and multivariable analyses. Indeed, it should be addressed that the pregnant cancer population features multiple risk factors influencing fetal growth irrespective of the antenatal treatment, including maternal stress, fatigue, hemodynamic changes, inflammation and malnutrition.[98,145] While the fetal genotype that determines the growth potential won't be affected, cancer is able to attack the developing fetus directly (by cancer treatment) and indirectly (by maternal psychological stress, oxidative stress and inflammation) by interfering with the in utero environment.[43] Growing evidence suggests histopathological, cellular and genotoxic changes in the placentas of pregnant cancer patients that will undeniably affect the capacity of the placenta to provide nutrients to the fetus.[74] The longer prenatal exposure to cancer and cancer treatment, the higher the impact on the growing fetus, is suggested in these data.

Pediatric reports support term delivery to avoid the associated risks of prematurity.[40 43,113] In this study we see an increase in gestational age of the last chemotherapy cycle of 3.3 days (95%CI [1.355-5.290]) for each 5-year period, what is slightly longer compared to our previous series (2.6 days [1.1 - 6.3]).[100] This has resulted in less preterm deliveries and thus less NICU admissions over time.[17] As a counterpart, in a high risk obstetric population, the risk of spontaneous preterm birth increases while awaiting term delivery. Besides antenatal chemotherapy, also other disease-related factors, such as cancer-induced inflammation and maternal stress, may directly cause preterm onset of labor and impact fetal growth. Therefore, pregnant patients should be monitored regularly by fetal ultrasound to evaluate for fetal growth. Based on clinical assessment and cervical

length measurement the individual risk of preterm delivery can be estimated. Physicians should be aware of potential medical complications during pregnancy, including maternal infections and VTE. Follow-up of these patients in centers with high risk obstetric and neonatal units and an experienced multidisciplinary team is recommended.

Using the INCIP database, we were able to assess obstetric outcomes in relation to detailed information on oncological diagnosis and treatment in a large group of pregnant cancer patients, whereas population-based studies often lack this detailed information or are limited in number because of the rarity of a cancer diagnosis in pregnancy. However, this is largely a retrospective data set, with inevitable missing or incomplete data. Poor maternal weight gain, a previously reported risk factor for low birthweight, was very frequently missing.[145] Miscarriages and stillbirths are likely to be underreported. Obstetric complications (pre-eclampsia, VTE,…), besides preterm spontaneous labor, are very likely to be underreported, hence we opted not to compare the incidences with the general population. Population-based studies are better tools to address these incidences. As routine registration of prenatal ultrasound information is lacking in the INCIP database, we were only able to assess SGA in this cohort, and not intrauterine growth restriction, a more reliable proxy for fetal growth.[145]

As reported here, the changes in policy that are made to continue pregnancies complicated by cancer, result in more livebirths with a downside of an increased risk of adverse obstetrical complications. Knowledge of risk factors including the use of chemotherapy and targeted or immunomodulatory therapies, cancer stage and maternal nutritional status is essential to tailor the obstetric follow up. The Advisory Board on Cancer Infertility and Pregnancy (www.ab-cip.org) aims to guide clinicians in formulating such follow-up as the clinical setting can be challenging and experience limited.[162] Indeed, the care for pregnant cancer patients requires a constant balance of maternal and fetal risks. Undeniably, obstetric management should not be guided solely by the pursuit of a full term delivery, but should be based on continuous risk assessment in case maternal or fetal deterioration occurs.

Chapter II - Subanalysis by cancer type

This chapter includes obstetric outcomes of pregnant women diagnosed with Hodgkin lymphoma, non-Hodgkin lymphoma, leukemia, bladder and renal cancer, and gastric cancer, registered by the International Network on Cancer, Infertility and Pregnancy (INCIP). Prior to this thesis, manuscripts on other common cancer types diagnosed during pregnancy were already published by INCIP. This is an overview of INCIP publications on:

- Breast cancer
  Loibl S, Han SN, von Minckwitz G, et al. Treatment of breast cancer during pregnancy: an observational study. Lancet Oncol 2012;13:887-96.[54]
- Cervical cancer
  Halaska MJ, Uzan C, Han SN, et al. Characteristics of patients with cervical cancer during pregnancy: a multicenter matched cohort study. An initiative from the International Network on Cancer, Infertility and Pregnancy. Int J Gynecol Cancer 2019.[163]
- Ovarian cancer
  de Haan J, Verheecke M, Amant F. Management of ovarian cysts and cancer in pregnancy. Facts Views Vis Obgyn 2015;7:25-31.[164]
  This is a review paper. A cohort study on cases registered by INCIP will be performed by Fruscio.
- Colon cancer
  Kocian P, de Haan J, Cardonick EH, et al. Management and outcome of colorectal cancer during pregnancy: report of 41 cases. Acta Chir Belg 2018:1-10.[165]
- Melanoma
  de Haan J, Lok CA, de Groot CJ, et al. Melanoma during pregnancy: a report of 60 pregnancies complicated by melanoma. Melanoma Res 2017;27:218-23.[166]
- Thyroid cancer
  Boucek J, de Haan J, Halaska MJ, et al. Maternal and obstetrical outcome in 35 cases of well-differentiated thyroid carcinoma during pregnancy. Laryngoscope 2017.[167]
- Brain tumors
  Verheecke M, Halaska MJ, Lok CA, et al. Primary brain tumours, meningiomas and brain metastases in pregnancy: report on 27 cases and review of literature. Eur J Cancer 2014;50:1462-71.[168]
- Lung cancer
  Boussios S, Han SN, Fruscio R, et al. Lung cancer in pregnancy: report of nine cases from an international collaborative study. Lung Cancer 2013;82:499-505.[169]

An overview of the main obstetric and neonatal outcomes of women with cancer diagnosis during pregnancy by cancer type (breast cancer, cervical cancer, lymphoma, leukemia, ovarian invasive cancer, borderline ovarian tumor, gastro-intestinal cancer, melanoma, thyroid cancer, brain tumor), included in the final analysis of this thesis on 2172 cases, can be found in Supplementary data page 43.

Chapter II.1. - Obstetric and maternal outcomes in patients diagnosed with Hodgkin lymphoma during pregnancy: a multicenter, retrospective, cohort study

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The obstetric outcomes of pregnant women diagnosed with Hodgkin lymphoma can be found in PART IV - Chapter VIII (p.159). This manuscript incorporates both obstetric outcomes and maternal survival of 134 patients diagnosed with Hodgkin lymphoma during pregnancy.

Chapter II.2. - Obstetric and maternal outcome in 80 patients diagnosed with Non-Hodgkin lymphoma during pregnancy

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Abstract

Objectives

This retrospective cohort study of the International Network on Cancer, Infertility and Pregnancy (INCIP) reports the obstetric and maternal outcomes of pregnant patients diagnosed with non-Hodgkin lymphoma (NHL).

Methods

Clinical data of 80 pregnant NHL patients diagnosed between 1986 and 2019 were analyzed, focusing on obstetric and maternal outcome of patients with diffuse large B-cell lymphoma (DLBCL).

Results

DLBCL was the most common NHL subtype (57 of 80, 71%). Fifty-four of 80 (68%) pregnant patients received chemotherapy, mostly CHOP-like (cyclophosphamide, doxorubicin, vincristine, prednisone) regimens (89%). Four early pregnancies were terminated and there was one stillbirth among 76 ongoing pregnancies (1.3%). Compared to patients who were not treated during pregnancy, antenatal chemotherapy appeared not to impact the incidence of preterm delivery (overall 52%), obstetric complications (overall 41%), neonatal complications (overall 12.5%) or small for gestational age neonates (SGA) (overall 39%). Half of preterm deliveries (18 of 39, 46%) were planned in order to tailor oncological treatment. The 3-year progression-free (PFS) and overall survival (OS) for DLBCL patients was 77.5% and 90.0%, respectively. Three-year PFS and OS for DLBCL patients treated with rituximab-CHOP was 83.4% and 95.% for limited stage (n=29) and 60.6% and 73.3% for advanced stage (n=15). Antenatal rituximab (n=36) appeared safe for both mother and child.

Conclusion

Standard treatment for DLBCL, including rituximab, can be offered to pregnant patients, with reassuring outcomes. Management of pregnant NHL patients should be organized in a high-risk obstetric center because of the high incidence of preterm delivery, complications and SGA neonates.

Introduction

With worldwide over 509000 reported cases in 2018, non-Hodgkin lymphoma (NHL) account for approximately 6% of all new cancer cases per year.[170] Diffuse large B cell lymphoma (DLBCL) is the most common NHL subtype, diagnosed in approximately 30-50% of cases. Mature T-cell and NK-cell neoplasms are uncommon and the incidence of the different subtypes varies greatly per geographic region and ethnic group. In accordance with the age distribution, non-Hodgkin lymphoma is diagnosed less frequently in pregnancy than Hodgkin lymphoma (respectively 5.39 versus 8.06 per 100,000 births).[24,25] A recent large population-based study demonstrated a rising prevalence over time, from 4.44 to 7.17 per 100,000 births over 9-year period, which can be explained by the trend of delaying first childbirth and the age-dependent increased incidence of NHL.[25,171]

Management depends on NHL subtype and stage. For curative B cell lymphomas, CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) with rituximab (R-CHOP), a CD20 monoclonal antibody, with or without radiotherapy is the standard of care.[172] Gestational age at diagnosis and the urgency of treatment contribute to the management in pregnant patients. Some consensus exist to defer treatment until after delivery in well selected cases of indolent NHL (e.g. follicular lymphoma (FL) grade 1-3A).[3,173] However, based on a literature search study of 121 patients pregnancy-associated NHL is suggested to be characterized by advanced stages, where immediate treatment is indicated.[174] Decision-making in pregnant patients is extremely challenging, especially in early pregnancy. To date, steroids or vinblastine, although not recommended as single agent for NHL, are suggested as a reasonable 'bridging treatment' until the second trimester of pregnancy, when chemotherapy can be initiated.[173] Compared to breast cancer, literature on the antenatal treatment for NHL is scarce.[85,141,175] Nevertheless, the most commonly used 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/m2, doxorubicin 60 mg/m2).[4] Although corticosteroids are given at higher equivalent dose in CHOP compared to AC, in which corticosteroids are given as antiemetic, antenatal CHOP may be equally safe. Experience with antenatal rituximab in the context of NHL is based on a series of 24 women giving livebirths with reassuring outcomes.[3,63]

By assessing all non-Hodgkin lymphoma cases registered by the international network on cancer, infertility and pregnancy (INCIP), we aimed to gain more insight into (1) the obstetric and neonatal outcome of CHOP-like regimens, with or without rituximab, during pregnancy, and (2) maternal outcome of NHL. We selected all patients with DLBCL for an in-depth analysis. For survival analysis we focused on patients treated with standard R-CHOP.

Methods

In 2005 an international registry cohort for all cancers diagnosed in association with pregnancy was launched by INCIP, supported by ESGO (the European Society of Gynaecological Oncology). The database consists of oncological and obstetric data, voluntarily registered by members of INCIP. This study was approved by the Ethical Committee of University Hospital Leuven (Belgian number B322201421061) and approval was obtained from the participating centers when indicated.

We retrieved all patients diagnosed with NHL during pregnancy 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 Ann Arbor staged and treated according to the local protocols of the participating centers. The criteria of the International Prognostic Index for aggressive NHL (DLBCL, anaplastic large cell lymphoma, peripheral T-cell lymphoma and extranodal natural killer T-cell lymphoma) were not reported because of the large number of missing values.[176] Obstetric and neonatal outcomes were reviewed if available. Patients that exclusively received antenatal radiotherapy were reported separately, as this approach is no longer recommended. According to current guidelines radiation therapy (when indicated) is administered after induction polychemotherapy and preferentially is initiated postpartum to avoid fetal harm.[3,172] Stillbirths were excluded for analysis of obstetric outcome. The neonatal and obstetric outcome of chemotherapy-exposed neonates was compared with non-exposed neonates. Outcomes of DLBCL patients, the largest subgroup, were reported separately. Small for gestational age (SGA) was defined as a birthweight below the 10th customized percentile corrected for gestational age, sex, maternal height, maternal weight, ethnicity and parity.[177]

Patients diagnosed with DLBCL, ongoing pregnancies and available follow-up were included for survival analysis. There were no patients with primary refractory disease. For DLBCL patients treated with standard R-CHOP-like treatment [R-CHOP or R-EPOCH (rituximab, etoposide, prednisolone, vincristine, cyclophosphamide, doxorubicin)] the maternal outcome was reported according to the stage at diagnosis (limited stage I-II versus 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 measured from the interval between diagnosis and death from any cause. To assess risk factors for adverse maternal outcome, univariate analyses were performed. The retrospective nature of the registry did not allow assessment of initial performance or functional status. Data were collected in a Microsoft SQL Server Database. We used the Fisher 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 IBM SPSS Statistics version 24. Two sided p values of 0.05 or less were considered significant.

Results

Clinical characteristics

Clinical characteristics of 80 patients with NHL diagnosis during pregnancy between 1986 and 2019 are shown in Table 1. Median age at diagnosis was 32 years (range 16-41). 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 (6 of 80, 8%). Extranodal disease was common (42%). Nine (26%) patients, 8 with DLBCL and 1 with Burkitt lymphoma (BL), had reproductive organ involvement of breast (n=7), uterus (n=1) and vulva (n=1).

Table 1: Clinical characteristics of patients diagnosed with Non-Hodgkin lymphoma during pregnancy

Characteristics	All Patients (n=80)		DLBCL (n=57)*	
	No.	%	No.	%
Age at diagnosis (median, range, IQR)	32; 16-41; 7		32.0; 16-40; 7.5	
<21	8	10.0	5	8.8
21-25	5	6.3	4	7.0
26-30	22	27.5	15	26.3
31-35	30	37.5	22	38.6
>35	15	18.8	11	19.3
Gestational age at diagnosis (weeks) (median; range; IQR)	22; 1-38; 10		22; 1-38; 9	
First trimester				
Second trimester	9	11.3	5	8.8
Third trimester	54	67.5	40	70.2
	17	21.3	12	21.1
Non-Hodgkin lymphoma (WHO, 2008)				
Follicular lymphoma	6	7.5		
Diffuse large B-cell lymphoma	57	71.3	57	100
Primary mediastinal B-cell lymphoma	12	15.0	12	21.1
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 or not reported	4	5.1		
Prior Pregnancies				
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				
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				
Yes	47	58.8	22	38.6
No	28	35.0	31	54.4
Not reported	5	6.3	4	7.0
Bulky Disease				
Yes	12	15.0	11	19.3
No	67	83.8	45	78.9
Not reported	1	1.3	1	1.8
Extranodal disease				
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				
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 chemo after delivery	*9*		*39.1*	*3*		*27.3*
Chemotherapy	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
Radiation therapy	3		3.8	0		0
Rituximab during pregnancy	36		45.0	33		57.9
Pregnancy outcome						
Live birth	75		93.8	56		98.2
Stillbirth	1		5	0		0
Termination of pregnancy	4		1.3	1		1.8
Preterm delivery*	39		52.0	29		51.8
Follow-up of patients (mean; range; IQR)	51.5; 1-358; 58			37.8;1-184; 48		
Complete remission	55		68.8	42		73.7
Recurrent disease	9		11.3	6		10.5
Deceased	9		11.3	5		8.8
Lost in follow-up after delivery	7		8.8	4		7.0

* Only including live births
** Doxorubicin monotherapy, MACOP-B, VACOP-B, R-ACVPB
[$]including one dose-adjusted approach EPOCH
Abbreviations: NHL: non-Hodgkin Lymphoma; IQR: Interquartile Range; NK: Natural Killer
(R-)CHOP: (rituximab-) cyclophosphamide, doxorubicin, vincristine
(R-)EPOCH: (rituximab-) etoposide, vincristine, cyclophosphamide, doxorubicin
MACOP-B: methotrexate (not given during pregnancy), doxorubicin, cyclophosphamide, vincristine, bleomycine
VACOP-B: etoposide, doxorubicin, cyclophosphamide, vincristine, bleomycine
R-ACVPB: rituximab, doxorubicin, cyclophosphamide, vindesine, bleomycin

Management

Three patients with aggressive NHL 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) radiation therapy in the second trimester of pregnancy (Table SII-II.2.2). Three other patients with BL were treated with chemotherapy, of whom one patient first had a planned preterm delivery. All patients with indolent NHL (6 with FL and 1 with Hairy cell leukemia) started with treatment after pregnancy termination (n=1) or delivery (median 12 weeks, range 2-32 weeks). In total, 54 (68%) NHL patients were treated with chemotherapy from the second trimester of pregnancy onwards and over the years more patients initiated chemotherapy during pregnancy (Table SII-II.2.1 and Figure SII-II.2.1). For 46 pregnant DLBCL patients 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).

Obstetric outcome

Seventy-five ongoing pregnancies (all NHL subtypes) ended in a live birth. Therapy planning was the main reason for planned preterm deliveries (18 of 39, 46% , Table SII-II.2.3). One pregnancy ended in a stillbirth after extensive vaginal bleeding, suggestive for placental abruption, prior to initiation of cancer treatment. 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=1.000, Table SII-II.2.4). Thirteen pregnant patients (23%) that initiated

chemotherapy had spontaneous preterm labor (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 SII-II.2.4).

Neonatal outcome

Two children prenatally exposed to R-CHOP after the first trimester of pregnancy, were born with an anomaly (a ventricular septum defect (VSD), and duplex right kidney), resulting in a congenital malformation rate of 2.9% (2 of 70 neonates with known outcome) (Table SII-II.2.5).

Table 2. Neonatal outcome of children born from patients with NHL*

Neonatal outcome	All (n=72)		DLBCL						p-value
			All (n=56)		Chemotherapy (n=46)		No antenatal treatment (n=10)		
	No	%	No	%	No	%	No	%	
Gestational Age at delivery									0.692
$37^{0/7} – 41$	35	48.6	27	48.2	22	47.8	5	50.0	
$34^{0/7} – 36^{6/7}$	21	29.2	19	33.9	17	37.0	2	20.0	
$32^{0/7} – 33^{6/7}$	12	16.7	6	10.7	4	8.7	2	20.0	
$28^{0/7} – 31^{6/7}$	4	5.6	4	7.1	3	6.5	1	10.0	
Birthweight (gram)									0.789
<2000	9	13.0	7	13.0	5	11.4	2	20.0	
2000-2499	23	33.3	19	35.2	15	34.1	4	40.0	
2500-2999	25	36.2	21	38.9	18	40.9	3	30.0	
>3000	12	17.4	7	13.0	6	13.6	1	10.0	
missing	3		2		2		0		
Birthweight Percentile									0.672
- <P10	28	38.9	24	44.4	20	45.5	4	40.0	
- P10-P24	9	12.5	6	11.1	4	9.1	2	20.0	
- P25-P49	14	19.4	13	24.1	12	27.3	1	10.0	
- P50-P74	12	16.7	7	13.0	5	11.4	2	20.0	
- P75-P90	1	1.4	0	0	0	0	0	0	
- >P90	5	6.9	4	7.4	3	6.8	1	10.0	
- missing	3		2		2		0		
Major congenital malformations									1.000
Yes									
No	2	3.0	1	1.9	1	2.4	0	0	
Missing	65	97.0	51	98.1	41	97.6	10	100.0	
	5		4		4		0		
Major neonatal complications**									1.000
Yes									
No	9	13.6	7	13.5	6	14.3	1	10.0	
Missing	57	86.4	45	86.5	36	85.7	9	90.0	
	6		4		4		0		
NICU admission									1.000
Yes	22	33.8	17	33.3	14	34.1	3	30.0	
No	42	64.6	34	66.7	27	65.9	7	70.0	
Missing	7		5		5		0		

Abbreviations: NICU: Neonatal Intensive Care Unit; SGA: small for gestational age
* Analysis of all live births, excluding 3 neonates prenatally exposed to radiation therapy
** including neonatal death, Idiopathic Respiratory Distress Syndrome (IRDS), neonatal sepsis, neutropenia, reversible reduced ejection fraction and neutropenia.

In total 24 of 56 neonates (44.4%) of patients diagnosed with DLBCL were SGA (Table 2). Birth weight percentiles in 46 children prenatally exposed to cancer treatment did not differ statistically from 10 non-exposed children (p=0.672). The results are similar for the entire cohort (54 chemotherapy-exposed versus 18 non-exposed; p=0.215, *data not shown*). Further sub-analysis did not reveal a difference in birthweight percentiles according to DLBCL stage or the receipt of antenatal rituximab (p=0.077 and p=0.673, respectively).

Major neonatal complications and admissions in neonatal Intensive Care Unit were comparable for chemotherapy-exposed and non-exposed neonates (Table SII-II.2.6). Prematurity was the main reason for NICU admission (15 of 17, 88%).

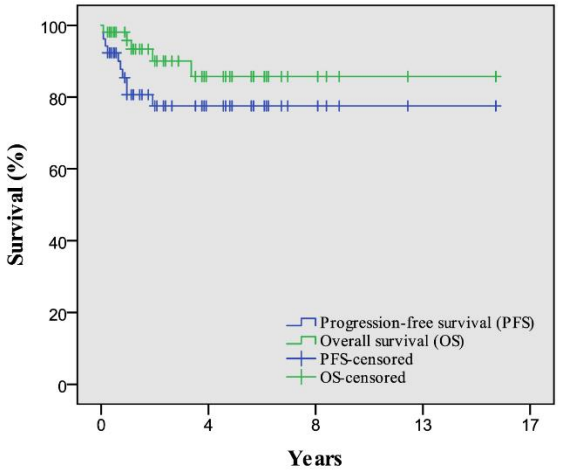
One infant, prenatally exposed to R-CHOP and born at 32 weeks of gestation, deceased at 9 days of life due to sepsis. Five out of 36 neonates prenatally exposed to rituximab were admitted to the NICU with prematurity-related complications. Two out of five neonates prenatally exposed to etoposide-based chemotherapy, delivered at 35 and 37 weeks of gestation, experienced respiratory difficulties, requiring NICU admission.

Maternal outcome

With a median follow-up of 38 months (range 1-184) 52 pregnant patients with DLBCL had a 3-year PFS and OS of 77.5% and 90.0%, respectively (Figure 1). 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 (Figure 2A). For advanced stage (n=15), 3-year PFS and OS were 60.6% and 73.3%, respectively (Figure 2B). The association of rituximab in 17 limited stage DLBCL pregnant patients treated with CHOP resulted in an excellent survival (PFS 91.7% and OS 100.0%) compared to 7 patients 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) also 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. Median treatment delay was 24 weeks (range 20-26) and median follow-up was 12 months (range 6-14). None of these 7 patients relapsed or died. Several variables were analyzed in univariate analyses in order to define factors that could predict outcome for 52 pregnant patients diagnosed with DLBCL (Table SII-II.2.7). The receipt of chemotherapy during pregnancy, the interval between diagnosis and treatment initiation nor the gestational age at diagnosis were risk factors for disease-free or overall survival.

Figure 1: Progression-free survival (PFS) and overall survival (OS) of patients diagnosed with DLBCL during pregnancy (n=52). Patients who terminated pregnancy prior to treatment initiation were excluded. 3-year PFS and OS of 52 pregnant patients with DLBCL is 77.5% and 90.0% respectively

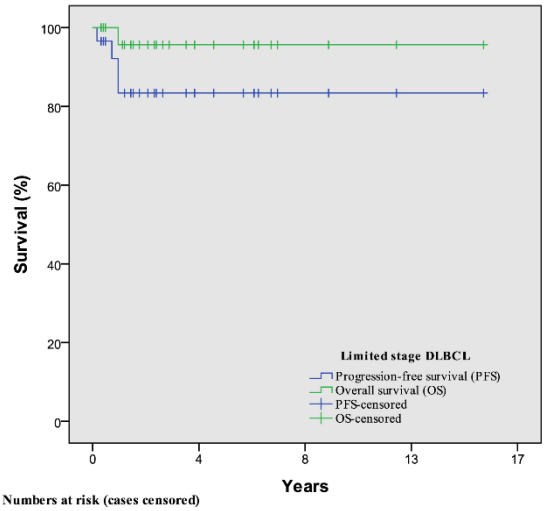


Number at risk (cases censored)

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

Figure 2: Progression-free survival (PFS) and overall survival (OS) of limited and advanced stage NHL treated with R-CHOP-like regimens. 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).

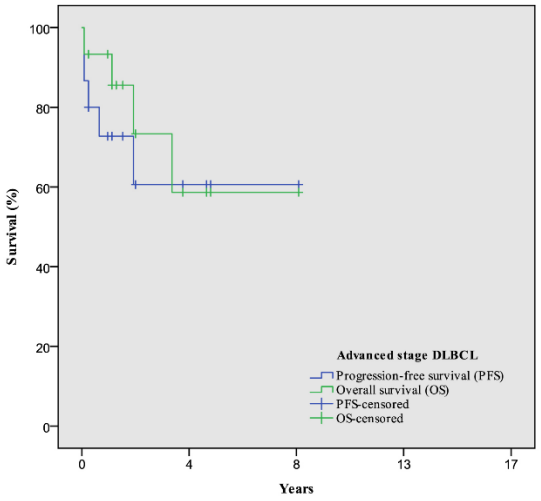
A. Limited Stage



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)

B. Advanced Stage



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)

Discussion

Here, we report the obstetric and maternal outcome of 80 pregnant patients diagnosed with NHL between 1986 and 2019, with an in-depth analysis on 57 patients diagnosed with DLBCL. Most patients initiated chemotherapy during pregnancy (68%) with a rising trend over time. Overall, the incidence of preterm delivery (52%), obstetric (41%) and neonatal (12.5%) complications and SGA-neonates (39%) was high, however this was not explained by the receipt of antenatal chemotherapy. Therapy planning was the main reason for elective preterm delivery. The 3-year PFS and OS for 52 DLBCL patients was 77.5% and 90.0%, respectively and is comparable to the expected survival in the non-pregnant population. Albeit low numbers, pregnancy-related DLBCL treatment delay and the receipt of chemotherapy during pregnancy did not appear to impact maternal outcome. Antenatal administration of rituximab in combination with chemotherapy appeared to be safe for both mother and child.

A literature search study identified 121 pregnant patients from 74 papers diagnosed with NHL between 1967 and 2011.[174] Thirty-nine had BL and 39 had DLBCL (36%), at an predominantly advanced stage (85% vs. 62%, respectively). In contrast, Evens et al. published a multicenter cohort of 50 pregnant patients with NHL, including 28 DLBCL patients, and 40% had advanced disease.[85] Our 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 series (42%), with affected reproductive organs in 26.5% of patients.[174] This latter phenomenon might be explained by the increased blood supply during gestation or the presence of gestational hormonal receptors.[174]

A large population-based study, including 427 patients with pregnancy-associated NHL, reported high maternal and fetal morbidity and mortality rates compared to 7,916,388 controls: i.e. including increased risk for pre-eclampsia (6.3%), caesarean section (39.8%), preterm birth (17.1%), postpartum blood transfusions (15.7%) and maternal infections (1.17%).[25] However, this study did not included details on the gestational age or stage at diagnosis or the management. Also, histological NHL diagnosis was not specified in 81.5% of cases. This INCIP series confirmed a high incidence of complications, with a high rate of preterm delivery (52%). Evens et al. and Pinnix et al. (8 NHL pregnant patients) equally reported a preterm delivery rate of 50% and failed to demonstrate an increased risk of adverse outcomes for patients with antenatal treatment compared to patients with deferred treatment.[85,141] As preterm delivery is associated with neonatal comorbidities, including impaired neurocognitive function, elective preterm delivery is no longer advised, unless justified by maternal factors.[40] 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. Surprisingly, this series reports only one pregnant NHL patient with venous thromboembolism. The hypercoagulable state in this population demands for consideration of prophylactic low molecular weight heparins (LMWHs).[3] 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%.[178] This is probably explained by the desire for a controlled delivery in oncological patients. However, in general a vaginal delivery should be preferred, unless there are obstetric or medical contraindications.[5]

It is well established that pregnant cancer patients are at higher risk to deliver SGA-neonates and this risk appears to be associated with the receipt of antenatal chemotherapy.[100,160] The recent INCIP data on Hodgkin Lymphoma (HL) revealed an incidence of SGA of 21% and chemotherapy-exposed neonates had lower percentiles compared to non-exposed neonates (p=0.035).[160] A large cohort on different cancer types confirmed a high chemotherapy-associated incidence of SGA.[100] SGA appeared not be associated with antenatal chemotherapy exposure in this NHL series, however the high incidence (39%) is potentially reflecting the systemic nature of NHL with a poor maternal general health and nutritional status. Also medication use (i.e. corticosteroids) can contribute. We did not find an association between NHL stage and SGA. More prospective research including information on intra-uterine fetal growth, maternal risk factors and cumulative chemotherapy dosages will give a better insight in 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 low-risk DLBCL in young adults treated with R-CHOP event-free and overall survival is 79% and 93%, respectively.[172] Survival of 52 pregnant patients with DLBCL in this series was comparable, although not all of them were treated with standard CHOP, some of them had a pregnancy-related treatment delay. Maternal outcome remained reassuring for DLBCL patients treated with standard R-CHOP. Chemotherapy during pregnancy did not impact maternal outcome. Pinnix at al., only including 6 pregnant NHL patients, had similar findings.[141] Remarkably, no negative events were registered for seven DLBCL patients that chose deferral of treatment until after delivery. However, these results should be interpreted with caution because of the low numbers and limited follow-up. Based on the non-pregnant population, DLBCL treatment should ideally not be delayed for longer than 1 month in order not to impair survival.[179,180] 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.[3,63,181] Hence, its use can be considered, as it is expected to improve DLBCL survival rates by 15-20%.[172] The results of this series suggest a similar survival benefit for pregnant patients.

An important limitation of this study is it retrospective design. Apart from the low events rate for DLBCL, the low numbers included possibly explains why we could not identify risk factors for survival. Furthermore, no recommendations can be given with regard to the addition of etoposide for peripheral T-cell lymphoma or double hit lymphomas, as numbers were too low. Also, international nature of the data did not allow histopathological review. However, NHL during pregnancy is extremely rare, and retrospective cohort studies

are the only manner to investigate this population. Continuous international collaboration is encouraged and gives a better insight in the clinical aspects of the pregnant cancer population.

Conclusion

Treatment of DLBCL with CHOP-like regimens during pregnancy can be considered, with reassuring obstetric and maternal outcomes. Addition of rituximab to CHOP for DLBCL appears safe for both mother and child. Follow-up of pregnant NHL patients in a high risk obstetric unit is recommended as preterm delivery, disease-related SGA-neonates and prematurity-related neonatal complications are common.

Chapter II.3. - Obstetric and maternal outcome in patients diagnosed with leukemia during pregnancy: a retrospective cohort study of 109 cases

Abstract

Objectives

This retrospective cohort study of the International Network on Cancer, Infertility and Pregnancy (INCIP) reports the obstetric and maternal outcomes of pregnant patients diagnosed with leukemia in pregnancy.

Methods

Clinical data of 80 women with a primary diagnosis of acute myeloid (AML, n=38) or lymphatic (ALL, n=42) leukemia during pregnancy and 29 women with a diagnosis of chronic myeloid leukemia (CML) during pregnancy between 1997 and 2020, were retrieved from the INCIP database.

Results

For acute leukemia, most women (64%) initiated chemotherapy during pregnancy. Prematurity (67%), NICU admission (69%) and SGA (40%) were common. With a median follow-up of 13 months (range 1-219) 32 pregnant patients with ALL had a 3-year progression-free survival (PFS) and overall survival (OS) of 55% and 75%, respectively. With a median follow-up of 17 months, 39 pregnant patients with AML had a 3-year PFS and OS of 60% and 63%, respectively.

For CML, most women received targeted therapy (45%, mostly interferon and tyrosine kinase inhibitors) or chemotherapy (17%, mostly hydroxyurea) during pregnancy. Most pregnancies ended in a term delivery (58%) and there were no neonatal complications reported. With a median follow-up of 28 months, 20 pregnant patients with CML had a 3-year PFS and OS of 77% and 92%, respectively.

Conclusion

A diagnosis of leukemia during pregnancy is challenging and treatment in pregnancy can be considered balancing maternal prognosis and significant fetal risks of SGA and prematurity.

Introduction

Leukemia in pregnancy is very rare, however challenging because a diagnosis demands prompt therapy decision making, balancing risks of mother and the unborn child. The incidence of a diagnosis of leukemia during pregnancy is estimated to be between 0.4 and 2.4 per 100,000 pregnancies.[7,11,16,29] The majority of leukemias diagnosed during pregnancy are acute, including two thirds acute myeloid leukemia (AML) and one third acute lymphatic leukemia (ALL).[29,182] Chronic myeloid leukemia (CML) is less frequent, accounting for approximately 10% of leukemia cases diagnosis in pregnancy. The incidence is expected to rise following the rising global incidence of AML and CML, as well as the introduction of the non-invasive prenatal test (NIPT), that has the ability to detect hematological cancers in early pregnancy.[183]

The management of leukemia in pregnancy highly depends on gestational age at diagnosis. Because of the aggressive character, in early pregnancy a termination of pregnancy is justified, while later in pregnancy the initiation of treatment can be considered. For acute leukemia, chemotherapy regimens (conventional induction therapy is anthracycline-cytarabine based) are intense and aggressive, and during pregnancy the experience is very limited. The various therapeutic options that are available for CML patients during pregnancy are, in order of efficacy, tyrosine kinase inhibitors, interferon alpha, leukapheresis and hydroxyurea. Prenatal exposure of tyrosine kinase inhibitors (eg. Imatinib) for the treatment of CML in pregnancy have a risk of serious fetal malformations and may induce hypertension.[64,184] Interferon alpha might be less effective for the treatment of CML, however it does not cross the placental barrier and the risk of fetal adverse effects is lower compared to imatinib.[185]

The literature on obstetric and neonatal outcomes following leukemia during pregnancy is limited to case reports, case series, and only one population-based study, that does not provide information on prenatal treatment.[29] A diagnosis of acute leukemia in pregnancy increases the risk of maternal death, preterm delivery and intra-uterine fetal death.[29] Leukemia chemotherapy regimens are usually aggressive, putting the unborn child even more at risk of severe adverse outcomes. Chemotherapy exposure in the first trimester, during organogenesis, is associated with fetal malformations, notably daunorubicin causing cardiotoxicity and cytarabine causing limb malformations.[39,186] There is some evidence that both leukemia itself, as well as antenatal chemotherapy, increases the risk of fetal death.[187,188] By comparing fetal deaths in patients with AML who did and did not receive intrapartum chemotherapy, Horowitz et al. established that exposure to chemotherapy in pregnancy may induce still birth.[189] Some papers suggest that antenatal chemotherapy for acute leukemia is an independent risk factor for fetal growth restriction (FGR).[29,47,187,190,191] Although the literature on CML during pregnancy is even more scarce compared to acute leukemia, CML in pregnancy seems not to be associated with preterm birth, low birth weight, or abortion.[192]

By assessing all cases with a primary diagnosis of leukemia during pregnancy, registered by the international network on cancer, infertility and pregnancy (INCIP), we aimed to gain more insight into (1) the obstetric and neonatal outcome of women with a diagnosis of leukemia during pregnancy, with a focus on women who receive antenatal treatment and (2) maternal outcome of leukemia in pregnancy. We report the results according to oncological diagnosis: acute myeloid leukemia, acute lymphoblastic leukemia and chronic myeloid leukemia.

Methods

In 2005 an international registry cohort for all cancers diagnosed in association with pregnancy was launched by INCIP, supported by ESGO (the European Society of Gynaecological Oncology). The database consists of encoded oncological and obstetric data, voluntarily registered by members of INCIP. This study was approved by the Ethical Committee of University Hospital Leuven (Belgian number B322201421061) and approval was obtained from the participating centers when indicated. In total, 16 academic centers from 7 different countries (in order of numbers of inclusion: Mexico, Belgium, Russia, The Netherlands, USA, Italy and Germany) registered 109 patients with a primary diagnosis of leukemia during pregnancy. Clinical data regarding disease characteristics, diagnosis, treatment, obstetric complications, neonatal outcome and maternal survival were collected. All patients were treated according to the local protocols of the participating centers.

Delivery prior to 37 weeks of gestation was deemed to be preterm. Small for gestational age (SGA) for singletons was defined as a birthweight below the 10th percentile corrected for gestational age, sex, maternal height, maternal weight, ethnicity and parity.[177] Congenital malformations were defined according to Eurocat.[148] We defined stillbirth as a fetal death or loss that occurs after 20 weeks of pregnancy.[193] Neonatal death was defined as death within 28 days after live birth and maternal death as the number of women that died during pregnancy or within 42 days following pregnancy termination or delivery.[193,194] Progression-free survival (PFS) was calculated from the time of diagnosis to the time of disease relapse/progression or death. Overall survival (OS) was measured from the date of diagnosis to the date of death of any cause. Descriptive statistics were used to present oncological and obstetric data. Data were reported separately for AML, ALL and CML. Obstetric and neonatal outcomes (birthweight, obstetric complications, congenital malformations, neonatal complications and neonatal intensive care unit (NICU) admission) of pregnant women that received antenatal chemotherapy were compared to pregnant women that did not receive chemotherapy, using a Fisher exact or Mann Whitney U test, as appropriate. For this analysis we focused on ongoing singleton live births pregnancies, excluding twin pregnancies, miscarriages, pregnancy terminations and still births. Progression-free and overall survival were calculated according to the Kaplan Meier method. Statistical analysis was performed with IBM SPSS Statistics version 24. Two sided p values of 0.05 or less were considered significant.

Results

Clinical characteristics of 109 patients with a primary leukemia diagnosis during pregnancy are shown in Table 1. Median age at diagnosis was 28 years (range 14-40). Most patients were diagnosed between 13 and 24 weeks of gestation (43%) and were multiparous (71%). In total, 80 women were diagnosed with acute leukemia (38 ALL and 42 AML) and 29 with chronic leukemia (CML).

Table 1: Clinical characteristics of patients diagnosed with leukemia during pregnancy

Characteristics	All N=109	ALL N=38	AML N=42	CML N=29
	N (%)	N (%)	N (%)	N (%)
Age at diagnosis				
Median (range; IQR)	28 (14-40;9)	24(14-39;11)	29(16-40;8)	29(19-38;8)
Missing data	5	1	3	1
Gestational age at diagnosis (weeks) [median (range; IQR)]	21(0-39;14)	24(0-36;9)	21(0-39;17)	14(2-37;10)
<13 weeks	25 (23)	4 (11)	9 (21)	12 (41)
13-24 weeks	47 (43)	16 (42)	18 (43)	13 (45)
24-32 weeks	21 (19)	13 (34)	6 (14)	2 (7)
>32 weeks	16 (15)	5 (13)	9 (21)	2 (7)
Prior Pregnancies				
Nulliparous	30 (29)	10 (26)	16 (39)	4 (15)
Multiparous	75 (71)	27 (71)	25 (61)	23 (85)
Not reported	4	1	1	2
Treatment during pregnancy				
No treatment/cancer surveillance	20 (18)	5 (13)	6 (14)	9 (31)
Delivery to start treatment	12 (11)	4 (11)	7 (17)	1 (3)
Termination of pregnancy	5 (5)	1 (3)	3 (7)	1 (3)
Chemotherapy	53 (48)	24 (63)	24 (57)	5 (17)
Target therapy	15 (14)	1 (3)	1 (2)	13 (45)
Chemo- and target therapy	3 (3)	3 (8)	0 (0)	0 (0)
Radiotherapy	1 (1)	0 (0)	1 (2)	0 (0)
Delay to start treatment				
<7 days	54 (51)	22 (63)	27 (64)	5 (18)
8-14 days	20 (19)	7 (20)	8 (19)	5 (18)
15-21 days	6 (6)	2 (6)	1 (2)	3 (11)
22-28 days	0 (0)	0 (0)	0 (0)	0 (0)
>28 days	25 (24)	4 (11)	6 (14)	15 (54)
Missing data	4	3	0	1
Pregnancy outcome				
Live birth	93 (85)	35 (92)	31 (73)	27 (93)
Still birth	4 (4)	2 (5)	2 (5)	0 (0)
Termination of pregnancy	5 (5)	1 (3)	3 (7)	1 (3)
Miscarriage	7 (6)	0 (0)	6 (14)	1 (3)
Preterm delivery*	55 (60)	24 (69)	20 (67)	11 (42)
Follow-up of patients [median (range; IQR)], months	16(0-219;46)	13(1-219;31)	17(1-213;59)	28(1-123;71)
Complete remission	61 (67)	21 (66)	24 (62)	16 (80)
Recurrent disease	8 (9)	4 (13)	1 (3)	3 (15)
Deceased	22 (24)	7 (22)	14 (36)	1 (5)
Lost in follow-up after delivery	18	6	3	9

Abbreviations: IQR: interquartile range
* Only including singleton live births

Acute leukemia

Four women (1 with ALL, 3 with AML), diagnosed prior to 16 weeks of gestation, opted for pregnancy termination. Eleven women had a planned delivery (7/11 (64%) preterm) in order to initiate cancer treatment. In total, 11 women did not receive treatment during pregnancy: One patient, diagnosed at 35 weeks of gestation, opted for cancer surveillance, spontaneously delivered a healthy infant at 40 weeks, and initiated treatment after delivery. Five women experienced a miscarriage or fetal death within 2 weeks from cancer diagnosis. Another five women (gestational age at diagnosis 26 weeks, range 21-33) experienced obstetric complications (preterm spontaneous labor, n=2 or fetal distress, n=3), and preterm delivery (range 27-33 weeks), prior to cancer treatment. In total, 51 out of 80 women (64%) initiated polychemotherapy during pregnancy; most regimens consisting of cytarabine in combination with anthracyclines (Table SII-II.3.1). Four out of 9 (44%) women who received chemotherapy prior to 12 weeks of gestation experienced loss of pregnancy (prior to 22 weeks). Another pregnancy ended in fetal death at 26 weeks of gestation, 3 weeks after intiation of polychemotherapy (based on cytarabine and idarubicin) (see Table SII-II.3.6). In five women, targeted treatment (imatinib, n=2 or rituximab, n=3) was given. One women received radiotherapy of an extramedullary localisation of AML in the eye at 20 weeks, had a live birth at 40 weeks and initiated polychemotherapy thereafter (Table SII-II.3.2).

Table 2. Neonatal outcome of children born from patients with leukemia (all singleton live births, n=91)

Neonatal outcome	Total (n=91)	ALL (n=35)	AML (n=30)	CML (n=26)	Acute leukemia		
					Antenatal Chemo (n=45)	No antenatal chemo (n=20)	p-value
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	
GA at delivery							
$37^{0/7}$ – 41	36 (40)	11 (31)	10 (33)	15 (58)	14 (31)	7 (35)	0.367
$34^{0/7}$ – $36^{6/7}$	22 (24)	8 (23)	7 (23)	7 (27)	13 (29)	2 (10)	
$32^{0/7}$ – $33^{6/7}$	19 (21)	9 (26)	9 (30)	1 (4)	11 (24)	7 (35)	
$28^{0/7}$ – $31^{6/7}$	10 (11)	6 (17)	3 (10)	1 (4)	6 (1)	3 (15)	
<28 weeks	4 (4)	1 (3)	1 (3))	2 (7)	1 (1)	1 (5)	
Birth weight							
<P10	31 (37)	14 (48)	9 (30)	8 (32)	20 (48)	3 (18)	0.026
P10-P24	17 (20)	3 (10)	8 (27)	6 (24)	6 (14)	5 (29)	
P25-P49	12 (14)	6 (21)	2 (7)	4 (16)	7 (17)	1 (6)	
P50-P74	10 (12)	3 (10)	3 (10)	4 (16)	2 (5)	4 (24)	
P75-P90	8 (10)	0 (0)	6 (20)	2 (8)	5 (12)	1 (6)	
>P90	6 (7)	3 (10)	2 (7)	1 (4)	2 (5)	3 (18)	
missing	7	6	0	1	3	3	
SGA	31 (37)	14 (48)	9 (30)	8 (32)	20 (48)	3 (18)	0.042
NICU admission							
Yes	45 (56)	19 (66)	21 (72)	5 (22)	27 (66)	13 (76)	0.540
No	36 (44)	10 (34)	8 (28)	18 (78)	14 (34)	4 (24)	
Missing	10	6	1	3	4	3	
Neonatal complications							0.734
Yes	13 (16)	8 (29)	5 (17)	0 (0)	10 (25)	3 (18)	
No	68 (84)	20 (71)	24 (83)	24 (100)	30 (75)	14 (82)	
Missing	10	7	1	2	5	3	

Abbreviations: GA: gestational age, P: (birth weight) percentile; SGA: Small for gestational age; NICU: Neonatal Intensive Care Unit

In total, 66 (83%) pregnancies (1 twin) ended in a live birth, mostly preterm (67%). Two children were born with a major anomaly [a cardiopathy (not prenatally exposed to treatment), and facial dysmorphia (prenatally exposed to polychemotherapy)], resulting in a major congenital malformation rate of 3.4 % (in total 58 children with reported data) (Table SII-II.3.5). There were 2 children with plagiochephaly.

In total 23 of 58 neonates (40%) of neonates were SGA (Table 2 and Table SII-II.3.3). Antenatal exposure to polychemotherapy had a negative impact on birth weight percentiles (p=0.062). Admissions in neonatal Intensive Care Unit and reported neonatal complications was comparable for chemotherapy-exposed and non-exposed neonates (for details see Table SII-II.3.4). Prematurity was the main reason for NICU admission (38/40, 95%). One infant deceased 2 days after prenatal exposure to idarubicin and tretinoin and spontaneous extreme preterm delivery at 23 weeks 5 days (see Table SII-II.3.6). Two infants, prenatally exposed to polychemotherapy (HCVAD) and born at 32 and 36 weeks after spontaneous delivery, deceased from neonatal sepsis.

With a median follow-up of 13 months (range 1-219) 32 pregnant patients with ALL had a 3-year PFS and OS of 55% and 75%, respectively (Figure 1). With a median follow-up of 17 months (range 1-123) 39 pregnant patients with AML had a 3-year PFS and OS of 60% and 63%, respectively (Figure 1). Five out of 10 women (50%) who initiated treatment with a delay of more than 28 days from diagnosis deceased from disease within 11 months.

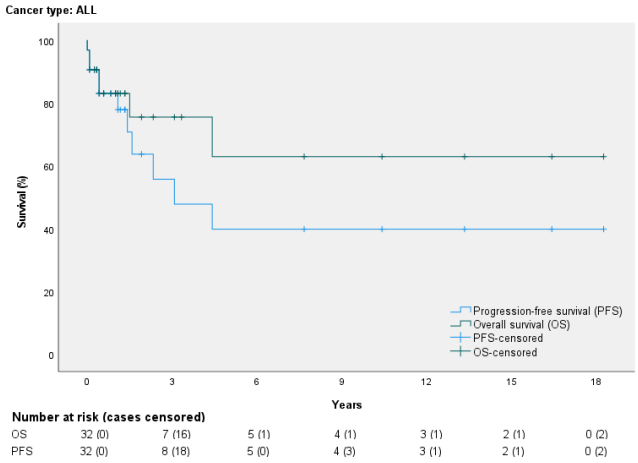
Chronic myeloid leukemia

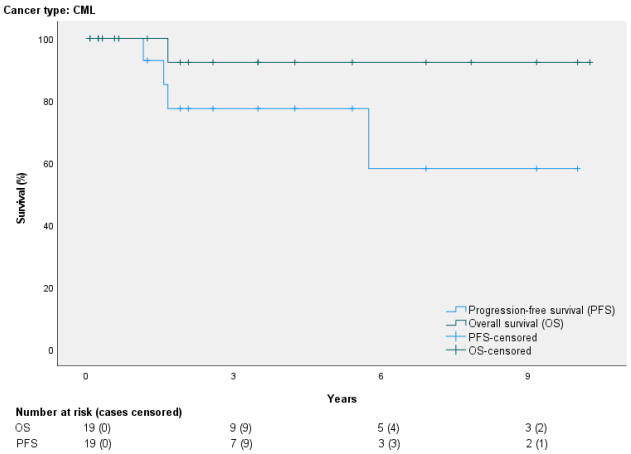
One woman diagnosed in early pregnancy, opted for pregnancy termination. One woman had an induction of labor at 38 weeks in order to initiate cancer treatment. In total, 9 women did not receive cancer treatment during pregnancy. One pregnancy ended in a late miscarriage at 17 weeks of gestation, 3 weeks after CML diagnosis. Three out of 8 women with ongoing pregnancies who opted for cancer surveillance (gestational age at diagnosis 15 weeks, range 11-20), experienced obstetric complications (preterm spontaneous labor, n=1 or fetal distress, n=2), and preterm delivery (range 27-36 weeks). In total, 18 women (62%) initiated treatment for CML during pregnancy. Most common regimens during pregnancy were interferon (n=7), tyrosine kinase inhibitors (n=5; imatinib or nilotinib (n=1)) or a combination thereof (n=1, with nilotinib). One patient received leukapheresis, prior to administration of interferon. In total, 5 women initiated with chemotherapy in pregnancy (most common hydroxyurea, see Table SII-II.3.1).

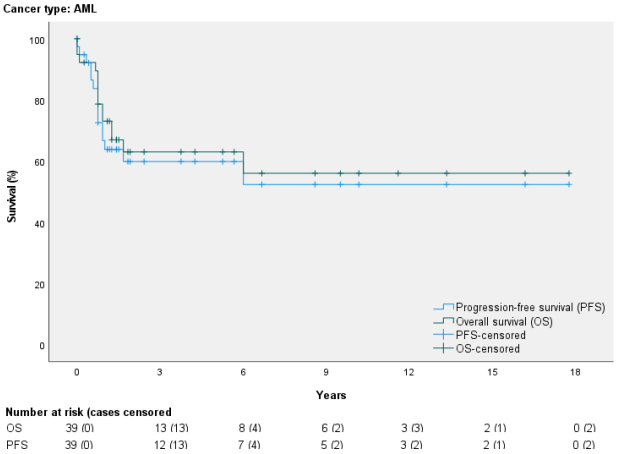
In total, 27 (93%) pregnancies (1 twin) ended in a live birth, 42% preterm. One neonate, prenatally exposed to imatinib, was diagnosed with pyloric stenosis at 1.6 months of age. There was no still birth, nor neonatal death reported. Eight out of 26 (32%) singleton live births were SGA. Prematurity was the main reason for NICU admission (4 out of 5).

With a median follow-up of 28 months (range 1-123) 20 pregnant patients with CML had a 3-year PFS and OS of 77% and 92%, respectively (Figure 1). One woman out of 15 who initiated treatment with a delay of more than 28 days from diagnosis, deceased from disease 20 months after diagnosis.

Figure 1: Progression-free survival (PFS) and overall survival (OS) of patients diagnosed with ALL, AML and CML during pregnancy.







Discussion and conclusion

Here, we report the obstetric and neonatal outcome of 80 women with a primary diagnosis of acute leukemia during pregnancy and 29 women with a diagnosis of CML during pregnancy between 1997 and 2020. For acute leukemia, most women (64%) initiated chemotherapy during pregnancy. Prematurity (67%), NICU admission (69%) and SGA (40%) were common. For CML, most women received targeted therapy (45%, mostly interferon and tyrosine kinase inhibitors) or chemotherapy (17%, mostly hydroxyurea) during pregnancy. Most pregnancies ended in a term delivery (58%) and there were no congenital malformations nor neonatal complications reported.

Because it aggressive nature, acute leukemia presents multiple medical and ethical challenges. In early pregnancy, termination of pregnancy, followed by conventional induction chemotherapy (cytarabine/anthracycline) is recommended.[3] When conservation of pregnancy is desired, future parents should be informed on fetal risks, such as preterm delivery and fetal growth restriction, when chemotherapy is administered during pregnancy.[39] Overall, cardiac function of neonates and children following prenatal exposure to anthracyclines appears to be clinically reassuring.[40,111,113] However awareness should continue as there appear to be some subtle changes in fractional shortening and left ventricular wall thickness in children exposed to fetal chemotherapy and there are some reports of cardiac impairment following prenatal exposure to lipophilic idarubicin.[195-197] Tretinoin, for example used in acute promyelocytic leukemia, is highly teratogenic in the first trimester of pregnancy, but can be administered thereafter. Methotrexate interferes with normal organogenesis and should be avoided prior to 20 weeks of gestation.[198] L-asparaginase increases the risk of thromboembolic events. Experience with tyrosine kinase inhibitors (such as imatinib), essential for patients with Philadephia chromosome-positive ALL, is still scarce.[64] Its crosses the placenta and its use should only be considered from the second trimester onwards, as exposure in the first trimester is associated with skeletal defects and urogenital malformations.[199] We report six cases with imatinib during pregnancy. Exposure was after 14 weeks of gestation in all cases and there was one infant with pyloric stenosis diagnosed at 1.6 months. There were no malformations reported in two infants prenatally exposed to nilotinib after 20 weeks of gestation.

In contrast to acute leukemia, CML demands lifelong treatment and patients may not only receive a diagnosis in pregnancy but may also (want to) become pregnant while on active treatment. Imatinib is highly effective for the treatment of CML, however prenatal exposure is associated with multiple congenital malformations, mostly skeletal, renal, respiratory and gastrointestinal. Exposure from the second trimester onwards can be considered on indication.[200] Leukapheresis and interferon, however less effective, are considered safe in pregnancy, regardless of gestational age. [3,185] Hydroxyurea, a cytotoxic agent that inhibits RNA synthesis, can be considered as an alternative when interferon does not induce good hematologic control. Its exposure in early pregnancy may induce craniofacial and spinal defects.[201]

The combination of pregnancy and leukemia increases the risk of both maternal and placental thrombotic events.[190,202] Theoretically leukemia cells cause an impaired nutrient exchange, blood flow, and oxygen delivery in the placenta which may lead to higher rates of fetal growth restriction, premature birth, and perinatal mortality. Most series on pregnant women with leukemia reported in the literature are observational and confirm the high incidence of preterm delivery, mostly planned for oncological reasons or fetal distress.[189,203,204] To date, the literature is sufficiently clear about the strong correlation between antenatal chemotherapy for leukemia and SGA.[190] Nolan et al, the first publication comparing the incidence of FGR between pregnant women with and without acute leukemia, did not reveal an association of leukemia and FGR (*however, the author does not mention how FGR is defined in methods*).[29] However, he latest INCIP analysis reveals that leukemia is an independent risk factor for SGA, when compared to pregnant women with breast cancer (see chapter 1 in this thesis). Of note, multiple factors, including co-mediation (steroids), psychological stress and poor nutritional status, contribute to impaired fetal growth in this high risk population.

Survival of acute and chronic leukemia in this series was comparable to previously published cohorts of women with leukemia in pregnancy.[204] Although the evidence is scarce, clinical data suggest a similar prognosis for women treated during pregnancy compared with non-pregnant patients.[190] Therapy delay or discontinuation to ensure pregnancy conservation or to strive for an optimal fetal outcome has been associated with adverse maternal outcome.[204-206]

Because pregnancy and leukemia rarely occur and clinical trial are not feasible in this population, knowledge from obstetric and neonatal outcome only comes from case reports, single and multi-center series and international registration. Large-scale data collection inevitable leads to missing data. Exact oncological treatment (eg. leukapheresisis or stem cell transplants, complete or partial response on chemotherapy) is often missing, hence not reported in this series.

Chapter II.4. - Renal and bladder cancer during pregnancy: a review of 47 cases and literature-based recommendations for management.

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Abstract

Objective

To provide contemporary gestational age-specific recommendations for management, a retrospective series of patients with renal or bladder cancer during pregnancy is reported.

Methods

Obstetric and oncological data of pregnant patients with a diagnosis of renal or bladder cancer were selected from the worldwide registry of the International Network of Cancer, Infertility and Pregnancy. In addition, the literature was reviewed for recent case reports since last reviews in 2014 for renal cancer and 2004 for bladder cancer.

Results

International Network of Cancer, Infertility and Pregnancy registered 22 cases (14 renal cancer and 8 bladder cancer), diagnosed between 1999 and 2017, and the literature reported 15 cases with renal cancer and 10 cases with bladder cancer between 2004 and 2019. Most common symptoms for renal and bladder cancer were pain (28%) and hematuria (66%), respectively. In more than half of the patients, surgical treatment was performed during pregnancy. Preterm deliveries were mostly medically induced (12 of 17, 71%) and all patients with a planned delivery before 34 weeks had advanced cancer. For renal and bladder cancer respectively, 79% and 87% of patients obtained complete remission. Advanced cancer stages had worse prognosis; 3 of 7 patients with known follow-up deceased within 15 months after diagnosis.

Conclusion

Gestational age at diagnosis determines further management of renal and bladder cancers during pregnancy. Advanced stages challenge decision-making. The maternal needs for immediate treatment, and the neonatal risks including the impact of a preterm delivery should be discussed in a multidisciplinary setting while respecting the patient's autonomy.

Introduction

The incidence of renal and bladder cancer in the general population is respectively 5.3 and 7.2 per 100.000.[207] Urological malignancies have a lower prevalence during the reproductive years, with a peak incidence, predominantly in males, occurring between 60 and 70 years of age. Obesity, smoking and hypertension are well-established risk factors for renal cell carcinoma. Bladder cancer is associated with exposure to cigarette smoking and chemicals (e.g. nitrosamine).[208] Screening for underlying hereditary cancer syndromes such as Lynch syndrome and Von Hippel-Lindau disease may be considered due to the young age at presentation. Urological cancer during pregnancy is extremely rare, affecting approximately 13 of 1.000.000 pregnancies.[7]

Signs of urological cancer such as hematuria, urgency, hypertension and low back pain may be attributed to pregnancy. In addition, the reluctance of performing imaging during pregnancy can lead to a delayed diagnosis.

Both the outcome for the pregnant patient and the unborn child must be taken into account in clinical decision-making, which is challenging and requires a multidisciplinary approach. The aim of this study is to give an overview of the obstetric and maternal outcomes of patients with a diagnosis of renal or bladder cancer during pregnancy and to provide gestational age-specific recommendations for management.

Materials and Methods

The International Network on Cancer, Infertility and Pregnancy (INCIP) (www.cancerinpregnancy.org), supported by the European Society of Gynecologic Oncology (ESGO), launched a registry of pregnant patients diagnosed with cancer. The study was approved by the ethical committee of the university hospitals of Leuven, Belgium and registered on ClinicalTrials.gov, number NCT00330447. Oncological and obstetric data of all patients diagnosed with primary or recurrent renal or bladder cancer during pregnancy were retrieved from the INCIP database. Patients diagnosed with cancer postpartum were excluded. Birth weight percentiles were determined using the customized calculator derived from www.gestation.net, adjusting for ethnicity, parity, height and weight of the mother, and gender of the neonate. Small for Gestational Age (SGA) was defined as a customized birth weight below the 10th percentile.

Retrieved INCIP cases were diagnosed between 1999 and 2017. In order to give an overview of most recent cases in the English literature from the same time period, a review of literature was performed using PUBMED. Articles were identified using the MESH terms 'Urological Neoplasms', 'Pregnancy', 'Renal Neoplasms' and 'Urinary Bladder Neoplasms', and variations hereof. For renal cases, case reports published since the latest review from 2014 were collected.[209] A recent Belgian case series of six pregnancy-associated renal malignancies was not included as reported cases were also included in the INCIP registry.[210] For bladder cancer all new cases published after the last large series (27 cases) in 2004 were reviewed.[211] Only descriptive statistics were performed. Obstetric outcome was reported for all cases, regardless of pregnancy outcome. The neonatal outcome of the INCIP cases was presented in detail.

Results

From the INCIP registry, 22 patients diagnosed with renal (n=14) or bladder cancer (n=8) during pregnancy were retrieved (Table SII-II.4.3 and 4.4). Patients were registered in eight different countries (Belgium, Italy, USA, Greece, Czech Republic, Mexico, Germany and the Netherlands). In the literature, 15 and 10 cases of renal and bladder cancer respectively, were reported since last large case series (Table SII-II.4.5 and 4.6).[193,194,212-231] Most symptomatic patients presented with loin pain (renal cancer) or hematuria (bladder cancer) (Table 1 and 2). In 16 patients (16 of 47, 34%) the tumor was detected while performing routine prenatal ultrasound.

Table 1: Characteristics of patients with renal cancer during pregnancy

	RENAL CANCER					
	INCIP Study population (n=14)		Case reports since 2014 (n=15)		All (n=29)	
	Number	%	Number	%	Number	%
Age at diagnosis (years),Median (range)	32 (22 – 37)		33 (22 – 46)		32 (22 - 46)	
Parity						
Nulliparous	5	35	3	20	8	28
Multiparous	8	57	6	40	14	48
Not reported	1	7	6	40	7	24
Smoking						
Yes	3	29	0	0	3	10
No	7	50	1	7	8	28
Not reported	4	21	14	93	18	62
Clinical presentation						
Hematuria	1	7	1	7	2	7
Pain	7	50	1	7	8	28
Hypertension	1	7	1	7	2	7
Incidental finding imaging	2	14	10	67	12	41
Persistent UTI	1	7	0	0	1	3
Fever	0	0	1	7	1	3
Hemorraghic shock	0	0	1	7	1	3
Not reported	2	14	0	0	2	7
Histopathology						
Renal cell carcinoma	11	79	14	93	25	86
Clear Cell	*7*	*64*	*6*	*43*	*13*	*52*
Papillary type	*0*	*0*	*3*	*21*	*3*	*12*
Chromophobe	*3*	*27*	*3*	*21*	*6*	*24*
Translocation type	*0*	*0*	*1*	*7*	*1*	*4*
Not reported	*1*	*9*	*1*	*1*	*2*	*8*
Nephroblastoma	1	7	0	0	1	3
Not reported	2	14	1	7	3	10
Stage at diagnosis						
Stage I	5	36	7	47	12	41
Stage II	5	36	4	27	9	31
Stage III	2	14	3	20	5	17
Stage IV	1	7	1	7	2	7
unknown	1	7	0	0	1	3
Gestational age at diagnosis, weeks (median, range)	18.2 (7 – 30)		16 (6 – term)		16.5 (6-term)	
Trimester of diagnosis						
First trimester	5	36	5	33	10	34
Second trimester	5	36	8	53	13	45
Third trimester	4	28	2	13	6	21
Management						
Antenatal treatment	8	57	9	60	17	59
Radical nephrectomy	*4*	*50*	*4*	*44*	*8*	*47*
Partial nephrectomy	*4*	*50*	*4*	*44*	*8*	*47*
Exploratory surgery	*0*	0	*1*	*11*	*1*	*6*
Postnatal treatment	6	43	6	40	12	41
Obstetric complications						
Hypertension	1	7	1	7	2	7

Pre-eclampsia	1	7	0	0	1	3
Gestational age at delivery, weeks (median, range)	38 (24 – 39)		35 (26 – 40)		37 (24 - 40)	
Obstetric outcome						
Live birth*	11	79	10	83	21	81
Termination	1	7	1	8	2	8
Miscarriage	1	7	0	0	1	4
Still birth	1	7	1	8	2	8
Not reported	0		3		3	
Oncological outcome						
Complete remission	10	100	5	55	15	79
Recurrent disease	0	0	2	22	2	11
Died due to disease	0	0	2	22	2	11
Lost in follow-up	4		6		10	
Maternal Follow-up, months (median, range)	33 (9-135)		17 (11 – 96)		30 (3-135)	

*Including one twin pregnancy. Abbreviations: ITU: urinary tract infection

Table 2: Characteristics of patients with bladder cancer during pregnancy

	BLADDER CANCER					
	INCIP Study population (n=8)		Case reports since 2004 (n=10)		All (n=18)	
	Number	%	Number	%	Number	%
Age at diagnosis (years) Median (range)	32 (28-36)		36 (28-39)		34 (28-39)	
Parity						
Nulliparous	4	50	4	40	8	44
Multiparous	4	50	5	50	9	50
Not reported	0	0	1	10	1	6
Smoking						
Yes	1	12	0	0	1	5
No	5	63	0	0	5	27
Not reported	2	25	10	100	12	67
Clinical presentation						
Hematuria	7	87	4	40	11	66
Incidental finding imaging	1	12	3	30	4	22
Vaginal bleeding	0	0	1	10	1	11
Abdominal pain	0	0	1	10	1	5
Asymptomatic bacteriuria	0	0	1	10	1	5
Histopathology						
Urothelial cell carcinoma	6	75	7	70	13	72
Adenocarcinoma	2	25	1	10	3	17
Squamous cell carcinoma	0	0	2	20	2	11
Stage at diagnosis						
TaN0M0	2	25	7	70	9	50
Stage I	1	12	0	0	1	6
Stage II	2	25	0	0	2	11
Stage III	1	12	0	0	1	6
Stage IV	1	12	1	10	2	11
Not reported	1	12	2	20	3	17
Gestational age at diagnosis, weeks (median, range)	23 (7– 35)		19 (9-26)		21 (7-35)	
Trimester of diagnosis						
First trimester	1	12	4	40	5	27
Second trimester	5	63	6	60	11	56
Third trimester	2	25	0	0	2	11
Management						
Antenatal treatment	4	50	6	60	10	56
TURBT	3	*75*	4	*67*	6	*60*
Partial Cystectomy	1	*25*	1	*17*	2	*20*
Chemotherapy(+TURBT)	0	*0*	1	*17*	1	*10*
Postnatal treatment	4	50	4	40	8	44
Obstetric complications						
PPROM	0	0	1	10	1	11
Postpartum hemorraghe	1	12	0	0	1	11
Gestational age at delivery, weeks (median, range)	36 (15 – 40)		38 (18 – 40)		37 (15 – 40)	

Obstetric outcome						
Live birth*	7	88	9	100	16	94
Termination	1	12	0	0	1	6
Not reported	0		1		1	
Maternal outcome						
Complete remission	6	86	7	87	13	87
Died due to disease	1	14	1	13	2	13
Lost to follow-up	1		2		3	
Maternal follow-up, months (median,range)	29 (4–197)		6 (1–24)		12	1-197)

*Including two twin pregnancies
Abbreviations: PPROM: Preterm Premature Rupture of Membranes; TURBT: Transurethral resection of bladder tumor

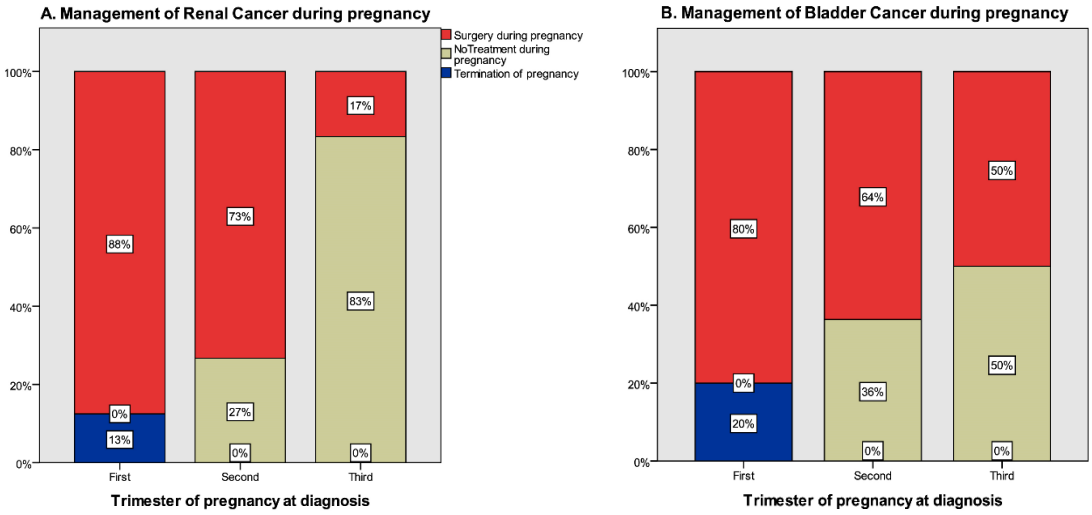
Oncological data

The management of renal and bladder cancer according to gestational age at diagnosis is presented in Figure 1. For 29 patients with renal cancer, the most common histological type of cancer diagnosed was clear cell type carcinoma (13, 45%) and the majority of patients presented with tumors limited to the kidney (stage I or II) (Table 1). Gestational age at elective surgery in 17 patients (59%) varied between 7 weeks and 29 weeks.
For 18 patients with bladder cancer, the most common subtype was urothelial cell carcinoma (UCC; 13, 72%) and half of patients (9,) had disease that did not infiltrate into the connective tissue or muscular layer of the bladder (TaN0M0) (Table 2). Surgical resection was performed between 10 and 39 weeks of gestation in 10 patients (56%); all were diagnostic trans-urethral resection of bladder tumor (TURBT) except one patient with an exploratory laparotomy with partial bladder resection of an urachal duct squamous cell carcinoma in early pregnancy.[225]

Obstetric outcome

Because of renal cancer diagnosis, two pregnancies were terminated in the first half of pregnancy. Another patient spontaneously miscarried after a nephrectomy for stage II renal cell carcinoma (RCC) at 7 weeks of gestation. Two patients diagnosed with renal cancer, had a stillbirth; One intra-uterine fetal demise occurred at 24 weeks of gestation, 1 month following laparotomy for renal cancer. Another patient presented with hemorrhagic shock secondary to spontaneous rupture of a renal tumor at term.[222] An emergency laparotomy could not prevent maternal and fetal death. The other 21 pregnancies (80%) with a reported obstetric outcome ended in a livebirth, including one twin pregnancy (Table 1). Ten out of 11 patients (91%) that delivered after 37 weeks underwent surgery during pregnancy. Eight of 10 patients (80%) delivered preterm for oncological reasons.

Figure 1: Management of renal (A) and bladder cancer (B) during pregnancy according to trimester of pregnancy at diagnosis. *One miscarriage occurred after a nephrectomy by laparotomy at 7 weeks of gestation. All other pregnancies diagnosed during the first trimester (n=7 for renal cancer and n=5 for bladder cancer), were operated between 10 and 17 weeks of gestation and ended in a live birth.*



For bladder cancer, there was one early pregnancy terminated for stage IV cancer. The 16 pregnancies (94%) with reported obstetric outcome ended in livebirths, including two twin pregnancies (Table 2). In 7 of 9 patients (78%) that delivered term prenatal surgery was performed. Four of 7 patients (57%) who delivered prior to 37 weeks had an elective delivery in order to initiate surgical or systemic treatment.

Neonatal outcome of INCIP cases

In the INCIP study population 17 singletons (excluding 1 set of twins) were born with a median gestation age at delivery of 37 weeks (range 32 – 40 weeks) (Table 1 and 2, see Table SII-II.4.1 and 4.2 for more details). Two out of 14 (14%) children with known birth weight were SGA. One neonate was born with tuberous sclerosis complex, a condition inherited from the mother who was diagnosed with RCC during pregnancy (case 2). Another neonate was born with bilateral club feet, after a pregnancy complicated with a TURBT for UCC of the bladder at 28 weeks of gestation. Reasons for neonatal hospitalization were prematurity (n=2), tuberous sclerosis (n=1) and hyperbilirubinemia (n=1). Twins were born after induction of labor at 32 weeks of gestation due to therapy planning for RCC. Both had low birth weight but were in good health.

Oncological outcome

For renal cancer, 15 of 19 patients (79%) with available follow-up were cured and had complete remission. One patient, diagnosed with stage III clear cell RCC, underwent immediate at time of diagnosis a cesarean section at 26 weeks of gestation for placenta previa, followed by radical nephrectomy.[221] One year later she developed lung metastasis. Another patient died from hemorrhagic shock due to renal cancer rupture as described above.[222] Six years after a diagnosis of stage II RCC, pulmonary metastasis were detected in another

patient in early pregnancy. After termination to initiate systemic therapy she progressed rapidly and died 6 months thereafter.[215]

For bladder cancer, 13 of 15 patients (87%) with available follow-up had a complete remission. Both patients with stage IV bladder cancer are deceased from disease. Eight months after diagnosis of advanced adenocarcinoma with uterine invasion, one patient suffered from omental metastasis and died a few months later. Another patient underwent a cesarean section followed by a radical cystectomy for a 10-cm bladder mass. She suffered from early disease recurrence in the pelvis with rapid progression and death.[230]

Comments

Renal cancer

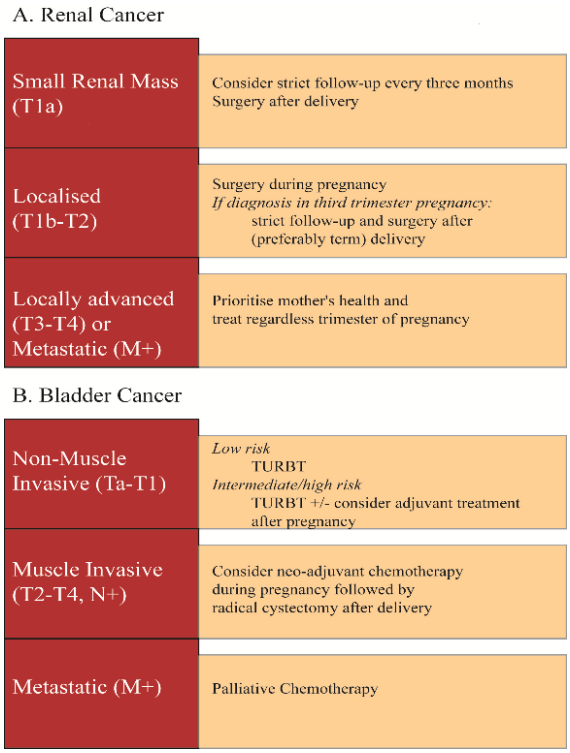
The most common renal cancer type during pregnancy is RCC. In the non-pregnant population, most patients present with a tumor confined to the kidney.[232] In this series, over half of pregnant patients were symptomatic and presented with tumors greater than 7 cm (stage II) or advanced (stage III or IV) disease. As clinical presentation might resemble pregnancy-related symptoms, a delayed diagnosis is plausible. It is speculative whether estrogens, who are elevated during pregnancy, might enhance tumor growth in renal cancers. Estrogen receptors are expressed in RCC cells and estrogen is shown to enhance RCC tumor growth in laboratory mice. [233] Different studies suggest that parity may increase the risk of developing a renal malignancy.[234] More research in humans is necessary to confirm this theoretical association.

After urinalysis, abdominal ultrasound should be considered without delay when a pregnant patient presents with loin pain or hematuria. Only consider imaging using radiation (e.g. Computed tomography (CT)) if results will change management. Below a threshold of 50 mGy no fetal adverse effects are reported, however a pelvic CT potentially exposes the fetus to higher doses and the radiation dose should be estimated in order to define fetal risks.[235] Magnetic resonance imaging (MRI) can be considered to differentiate and stage solid renal masses during all trimesters of pregnancy, with the advantage of avoiding fetal radiation exposure.[236] The use of the MRI contrast product, gadolinium, should be limited as it is associated with congenital malformations, nephrogenic systemic malformations and neurotoxic effects.[237]

Treatment of renal cancer during pregnancy depends on the stage of disease and may be further influenced by the trimester of pregnancy at diagnosis (Figure 2).[209] Surgery is the gold-standard procedure for the treatment of renal cancer in localized and locally advanced disease and in selected cases with low metastatic burden, especially in the young population.[209] During the first trimester the transabdominal surgical approach is feasible, whereas in later trimesters the retroperitoneal area is reached by retroperitoneal approach.

RCC's have a slow growing nature with reported doubling times with a range of 300 – 505 days. In case of *a small renal mass (SMR, cT1a, ≤4cm)* a renal biopsy and active surveillance (e.g. every 3 months) might be considered in well selected pregnant patients, according to similar tumor criteria as in the non-pregnant population.[238] Strict

Figure 2: Recommendations for management of renal (A) and bladder (B) cancer during pregnancy according to stage at diagnosis.



surveillance during pregnancy seems reasonable as the effect of pregnancy (or increased circulation of estrogens) on the course of renal cancer is still debated.[233,234]

When *a localized renal mass (cT1b-T2)* is diagnosed during pregnancy, surgical management can be considered if possible.[209]

When a diagnosis is made during the late third trimester, delivery should be planned in order to minimize therapeutic delay. If possible, term delivery (after 37 weeks) is the goal as a preterm delivery places the child at risk for impaired neurocognitive outcome.[40] If delivery is planned by caesarean section, simultaneous oncological surgery is possible.[209] All cases in this series with a diagnosis after 29 weeks underwent surgical treatment following a delivery beyond 35 weeks, except one twin pregnancy that was induced at 32 weeks.

In patients diagnosed with *locally advanced renal cancer* which invades adjacent structures (T3-4, N+) or *with distant metastasis* (M1) it is suggested to treat regardless of the trimester of pregnancy, as the mother's health should be prioritized.[209] The parents should be counselled on all treatment options, the fetal risks and potential impact on maternal oncological outcome for all scenarios, including termination of pregnancy or oncological treatment during pregnancy. First trimester exposure to Tyrosine kinase inhibitors (TKI), that can be used in the metastatic setting of renal cancer, is associated with spontaneous abortion and congenital malformations.[199] As safety data on the use of TKI (or other targeted or immunotherapy agents) during the second and third pregnancy is still limited to a dozen patients, solid recommendations are not possible at this time.[199]

In cohort studies including young patients diagnosed with renal cancer, the cancer specific 5-year survival varies between 78-88.4%.[232] The maternal outcome in pregnant patients diagnosed with renal cancer seems to be equivalent to that of non-pregnant patients.[209]

<u>Bladder cancer</u>

The most common bladder cancer type during pregnancy is UCC. Patients with bladder cancer usually present with hematuria.[211] Ultrasound can provide clues, but the diagnosis in pregnant patients can be missed. Cystoscopy is imperative in the diagnostic work-up of painless hematuria, in the absence of urinary infection. The treatment during pregnancy depends upon stage of disease and trimester of pregnancy.[211]

Patients diagnosed with *low-risk non-muscle invasive bladder cancer (NMIBC) [low grade pTa (diameter < 3 cm)]* can be successfully treated with TURBT followed by a surveillance cystoscopy at 3 months.[211] Patients with risk factors (pT1 (invasion of the lamina propria), high grade, diameter >3 cm, multifocal, carcinoma in situ) have a high risk of recurrence (up to 45.8%).[239] For these cases, immediate post-TURBT instillations or adjuvant therapy by intravesical immunotherapy [Bacillus-Calmette-Guérin (BCG)] or chemotherapy (Mitomycin) might be indicated, according to the guidelines of the European Association of Urology (EAU).[238] Local vesical toxicity (e.g. dysuria, frequency) is generally mild and transient, while systemic side effects range from mild symptoms to severe illness (e.g. sepsis, arthritis). Systemic absorption after intravesical

administration is limited for most agents as it depends on molecular weight of the drug (very limited if > 300 kDa), but increases with bladder damage (e.g. traumatic catheterization or recent bladder tumor resection). Experience with intravesical treatment during pregnancy is limited to two case reports (BCG and Mitomycin C).[194,240] Although normal fetal outcomes were reported in each, live vaccines (such as BCG) are contra-indicated during pregnancy and caution is warranted with the use of intravesical Mitomycin as it has the capacity to cross the placenta and is proven embryotoxic in animals.[241] Therefore, we believe that in intermediate or high risk NMIBC, strict clinical follow-up with (3-monthly) cystoscopy during pregnancy followed by intravesical BCG after pregnancy is reasonable. In patients with *muscle-invasive bladder carcinoma (MIBC), with or without lymph node involvement*, platinum-based neo-adjuvant chemotherapy is indicated, followed by radical surgery.[238] Depending on the gestational age at diagnosis, a termination of pregnancy or initiation of chemotherapy during pregnancy can be considered. With the use of cisplatinum dose-dependent neonatal hearing problems are described with doses higher than 70 mg/m^2.[40] Carboplatinum seems to be a safer alternative for the fetus. However, cisplatinum has proven to be more effective in bladder cancer and fetal risks should be balanced with maternal survival benefits in counselling.[238] Also other risks of chemotherapy during pregnancy, including preterm contractions and intra-uterine growth restriction should be discussed.[40,242] Due to the higher risk of blood loss explained by pelvic congestion, it is suggested to perform radical cystectomy 3-4 weeks after delivery. In case of *metastatic bladder cancer*, treatment options are restricted to palliative chemotherapy. The three patients with advanced bladder cancer in this series were diagnosed in the second trimester of pregnancy and underwent termination or preterm delivery (32 weeks) followed by radical treatment (case 18,19 and Alleemudder et al.).[230] Remarkably, one intermediate NIMBC INCIP case (with low grade T1N0) did not receive intravesical treatment postpartum following TURBT in pregnancy (case 15). However the retrospective character of the INCIP registry unavoidably misses or incorporates incorrect data.

Obstetric considerations

Surgery can be performed at any time during the course of pregnancy, however in very early pregnancy (the 2 weeks post conception) the" all-or-nothing" principle applies and patients should be counselled about the risk of early miscarriage.[242] During the late first trimester and the remainder of pregnancy, an adapted anesthetic approach to maximize maternal and fetal safety must be provided, including maintenance of stable oxygenation and blood pressure, avoidance of harmful drugs in early pregnancy, avoidance of preterm labor and optimal pain control. Spinal anesthesia can be considered as an alternative for general anesthesia. As monopolar TURBT has a higher risk of bladder perforation and other complications (including electrolyte abnormalities), the bipolar technique seems a safer alternative during pregnancy.[238] Over the years more cases of laparoscopic (or robotic) interventions for renal cancer during pregnancy are being published.[243] The advantages of these approaches, such as less blood loss and short hospitalization should outweigh the possible

risks such as uterine injury and hemodynamic changes secondary to increased intra-abdominal pressure. A laparoscopic approach can be considered by a surgical team with expertise during the first half of pregnancy (prior to 26 weeks), when the gravid uterus still enables surgical visibility. A priori, patients with urological malignancies can deliver vaginally if there are no other maternal or obstetric contraindications. In bulky tumors the theoretical risk of tumor spread when the neonates passes the birth canal should be discussed with the patient and weighed against the risk of bladder injury and tumor dissemination during caesarean section. In this case series, patients with tumors larger than 4 cm were all delivered by caesarean section.

Treatment goals should include postponement of delivery beyond 35-37 weeks of gestation, whenever possible, in order to safeguard neonatal outcome.[40]

Conclusions

Despite the rare occurrence of urological cancers during pregnancy, it should be included in the differential diagnosis when a pregnant patient presents with persistent urological complaints. Trimester of pregnancy and stage at diagnosis are most determinant in management. Surgery, if indicated and possible, can be considered safe in all three trimesters and enables term delivery with most optimal neonatal outcome. In the case of unresectable or advanced tumors, mother's health should be prioritized. If intravesical cytotoxic treatment is indicated, a strict follow-up with cystoscopy during pregnancy followed by postpartum treatment is reasonable, as experience during pregnancy is limited. In summary, urological cancer in pregnancy must be discussed case by case in a multidisciplinary setting, taking both mother's health, neonatal outcome and patient's perspective into account.

Chapter II.5. - Gastric cancer during pregnancy: a report on 13 cases and review of the literature with focus on chemotherapy during pregnancy

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Abstract

Introduction

Gastric cancer during pregnancy is extremely rare and data on optimal treatment and possible chemotherapeutic regimens are scarce. The aim of this study is to describe the obstetric and maternal outcome of patients suffering from gastric cancer during pregnancy and review the literature on antenatal chemotherapy for gastric cancer.

Material and methods

Treatment and outcome of patients registered in the INCIP database (International Network on Cancer, Infertility and Pregnancy) with gastric cancer diagnosed during pregnancy were analyzed.

Results

In total, 13 patients with gastric cancer during pregnancy were registered between 2002 and 2018. Median gestational age at diagnosis was 22 weeks (range 6 – 30 weeks). Twelve patients were diagnosed with advanced disease and deceased within 2 years after pregnancy, the majority even within 6 months. In total, 8 out of 10 live births ended in a preterm delivery because of pre-eclampsia, maternal deterioration or therapy planning. Two out of six patients that initiated chemotherapy during pregnancy delivered at term. Two neonates prenatally exposed to chemotherapy were growth restricted and one of them developed a systemic infection with brain abscess after preterm delivery for pre-eclampsia two weeks after chemotherapy. No malformations were reported.

Conclusions

The prognosis of gastric cancer during pregnancy is poor, mainly due to advanced disease at diagnosis, emphasizing the need for early diagnosis. Antenatal chemotherapy can be considered in order to reach fetal maturity, taking possible complications as growth restriction, preterm delivery and hematopoietic suppression at birth into account.

Introduction

Gastric cancer is one of the most common cancers, with very specific geographical, ethnic and socioeconomic differences in incidence. GLOBACAN (Global cancer observatory, WHO) data estimated about one million new patients in 2018.[170] More than 70% of gastric cancer cases occur in developing countries and the majority patients come from Eastern Asia. Known risk factors for gastric cancer include age, smoking, ethnicity and geography, history of gastric ulcer and immunosuppressive disease. Exposure to Helicobacter pylori plays a role in the development of non-cardiac cancer, whereas gastroesophageal reflux disease and obesity are risk factors especially for cardiac cancer. Typically gastric cancer has a male predominance and is diagnosed at a median age of 70 years, whereas only 1% of patients is younger than 34 years at diagnosis.[244] Pregnancy-associated gastric cancer, defined as a diagnosis of gastric cancer during pregnancy or up to 1 year after delivery, is estimated to complicate 0.026% to 0.1% of all pregnancies.[245]

Gastric cancer is staged according to the AJCC (American Joint Committee on Cancer) /UICC (Union for International Cancer Control) TNM staging system, based upon tumor size (T), lymph node invasion (N) and metastatic disease (M). Early gastric cancer is limited to the mucosa or submucosa (T1), whereas the tumor is assumed to be clinically localized once the muscular layer (T2) is invaded. Stage I gastric cancer is limited to the stomach, whereas in stage II lymph nodes are affected or the tumor has spread to the subserosa or serosa (T3-4aN0). In stage III the tumor invades both (sub)serosa and lymph nodes, in stage IV the tumor has spread to the adjacent organs with lymph nodes affected or distant organs. The stage distribution in the general population is 21.6% for stage I, 22.3% for stage II, 44.0% for stage III and 12.1% for stage IV.[246] Pregnant patients are at risk for delayed diagnosis of gastric cancer because symptoms may be regarded as gestational features and because of the reluctance to perform invasive diagnostic procedures such as gastroscopy.[247] As a result, gastric cancer is often diagnosed in more advanced cancer stages. Gastric cancer that invades through the submucosa stage II or higher) with no evidence of distant metastases, or locally advanced inoperable disease can be treated with curative intent by surgical resection and perioperative chemotherapy.[248] In locally advanced unresectable or metastatic gastric cancer, surgery is not a feasible option and palliative chemotherapy can be considered. Standard cytotoxic treatment for primary gastric cancer consists of a platinum-fluoropyrimidine based regimen, such as FOLFOX (5-Fluorouracil (5-FU), leucovorin and oxaliplatin), CAPOX (capecitabine, oxaliplatin) or ECF/ECC (epirubicin, cisplatin, 5-FU/capecitabine) or EOX (epirubicin, oxaliplatin, capecitabin). Trastuzumab combinations may be administered in case of HER2 overexpressing gastric cancers. Alternatively, taxane based schedules may be applied (FLOT (5-FU, leucovorin, oxaliplatin, docetaxel)).

Various chemotherapy regimens are feasible during pregnancy without an increased risk of congenital malformations if administered after the first trimester.[100] Nowadays, more pregnant patients with cancer are treated with chemotherapy in order not to delay treatment while avoiding preterm birth or pregnancy

termination as much as possible.[100] To date, the relative safety of antenatal chemotherapy is mainly demonstrated for treatments used in breast and cervical cancer and lymphomas, but experience with gastric cancer is limited. Most large case series on gastric cancer during pregnancy do not report on the use and consequences of cytotoxic treatment and include Asian patients only.[245,249,250] However, biological behavior and response to treatment may show geographic differences.[251] Therefore, we selected all patients with a diagnosis and/or treatment of gastric cancer during pregnancy from the international "cancer in pregnancy" INCIP registry (International Network on Cancer, Infertility and Pregnancy; www.cancerinpregnancy.org). We conducted a review of cases where chemotherapy was initiated during pregnancy and assessed neonatal outcome in this population.

Material and methods

All patients diagnosed with primary or recurrent gastric cancer during pregnancy were selected from the database of the International Cancer in Pregnancy registration study (Clinicaltrials.gov, number NTC00330447). The registry contains retrospectively and since 2005 prospectively collected oncological and obstetrical data of patients diagnosed with any pregnancy-associated malignancy. The registered cases are reported by physicians, INCIP members, with a special interest in cancer in young women. Currently the registry contains 2059 patients with a cancer diagnosis during pregnancy, registered by European (Belgium 25%, Netherlands 21%, Italy 13%, Czech republic 6%) and non-European centers (Philadelphia (USA) 13%, Russia 8%, Mexico 6%).For the present study patient data on treatment and obstetrical outcomes were collected. Referring physicians were contacted to complete missing data. Small for gestational age (SGA) was defined as a birthweight below the 10th percentile and percentiles were corrected for gestational age, sex, maternal height, maternal weight, ethnicity and parity, according to the calculator from the Gestation Network (www.gestation.net; v8.0.2, 2018) Preterm delivery was defined as birth before 37 weeks of gestational age.

In addition, we performed a narrative review and searched for case reports and case series, as well as articles on treatment options for gastric cancer during pregnancy, published in the English literature. Articles were identified by a PUBMED search with following MESH terms: 'pregnancy', 'gastric cancer' and 'chemotherapy' and variations hereof. For statistics, we used descriptive analysis. Comparative analysis was not performed because of the small number of patients.

The international registration study was approved by the Ethical Committee of University Hospitals of Leuven (B322201421061) and participating centers according to local policies.

Results

Patient and tumor characteristics

In total, 13 patients diagnosed with primary or recurrent gastric cancer during pregnancy were retrieved from the registry (Table SII-II.5.3). Patients were diagnosed between March 2002 and November

2017 in six countries (The Netherlands (n=5), USA (n=3), Belgium (n=2), Czech republic (n=1), Italy (n=1), and France (n=1)). One patient with a diagnosis of gastric carcinoma in situ treated with surgery and in remission 1 year prior to pregnancy was excluded.

All patients, except one, were diagnosed with advanced or metastatic disease (12/13, 92.3%). Patients' demographics are described in Table 1. Median maternal age at diagnosis was 32 years (range 26 -39 years), median gestational age at diagnosis was 21 weeks (range 6 – 30 weeks). Most patients were diagnosed with a diffuse type (signet ring cell carcinoma) gastric cancer. One patient was found to be pregnant on the computed tomography (CT) scan that was performed during trastuzumab maintenance therapy. This case highlights the importance of pregnancy testing as young patients can still be fertile despite amenorrhea secondary to cancer treatment. Most patients (9/13, 69%) presented with gastro-intestinal symptoms (nausea and vomiting (5/13, 39%), diarrhea (1/13, 8%), distended abdomen (3/13, 23%)). One patient presented with a palpable cervical adenopathy. Because the origin of the primary tumor was initially uncertain, she was initiated with carboplatin and paclitaxel during pregnancy and switched postpartum to cisplatin, doxorubicin and trastuzumab when CT scan revealed a gastric tumor. Another patient presented with vertebral pain caused by bone metastasis. Two patients had ascites, in combination with liver metastasis or peritoneal metastasis. Five patients were diagnosed with ovarian Krukenberg tumors.

Table 1: Patient characteristics

	Present cases (n(%))
Total number of cases	13
Age (years) (Median (range))	31.7 (26.9-39.9)
Gestational age at diagnosis (weeks)* (Median (range))	22(6 – 30)
Gestational age at delivery (weeks) (Median (range))	32(19- 39)
History of smoking	4 (31%)
Histopathology	
- Diffuse type	12 (100%)
o Signet ring-cell	8 (67%)
- Intestinal type	0
- unknown	1
Disease Stage at diagnosis	
- Stage II	1 (8%)
- Stage IV	12 (92%)
Treatment during pregnancy	
- Chemotherapy	6 (46%)
- Surgery with curative intent	1 (8%)
- Exploratory surgery (palliative)	
Deferral of treatment until after delivery	3 (23%)
	3 (23%)
Obstetrical outcome	
- Termination of pregnancy	1 (8%)
- Late miscarriage/IUD	2 (15%)
- Live birth	10 (77%)
< 28 weeks	1
< 34 weeks	5
< 37 weeks	2
Term	2
Complications	
- Pre-eclampsia	3 (23%)
- Spontaneous preterm delivery	1 (8%)
- Low birth weight (<P10)**	4 (44%)
Mode of delivery	
- Vaginal delivery	2 (20%)
- Cesarean section	8 (80%)
Placental metastasis	0
Maternal outcome	
Deceased during pregnancy	1 (8%)
Alive in 3 months	9 (69%)
Alive in 6 months	7 (54%)
Alive in 12 months or more	4 (31%)

*Excluded 1 patient with recurrent gastric cancer during pregnancy
** 1 case birth weight unknown
IUD: intra-uterine death (deceased with mother)

Surgical and chemotherapeutic management during pregnancy

One patient with stage II cancer started with chemotherapy at 23 weeks of gestation followed by curative gastrectomy after delivery. In total, 10 patients had ongoing pregnancies with inoperable gastric cancer and in 5 patients chemotherapy was initiated in the second trimester of pregnancy. The chemotherapeutic regimens used during pregnancy were: 5-FU, FOLFOX and carboplatin/paclitaxel. One patient underwent surgery with a curative intent but was diagnosed with intestinal metastasis peroperatively and initiated palliative chemotherapy after elective cesarean section at 32 weeks. Four patients received no definitive surgical or cytotoxic treatment during pregnancy aside from adnexectomies.

Obstetrical Outcome

As described in Table 1, there was one termination of pregnancy, two pregnancy losses and 10 live births. One patient pregnant with twins opted for a termination of pregnancy at 23 weeks of gestation because of metastatic disease. One patient died from the disease two weeks after diagnosis at 22 weeks of gestation. One patient miscarried at 19 weeks of gestation following an exploratory laparotomy and adnexectomy. Three patients underwent an emergency cesarean section for pre-eclampsia between 27 and 33 weeks of gestation. Another patient was delivered at 29 weeks of gestation by cesarean section because of clinical maternal deterioration. Four patients had an iatrogenic preterm delivery for therapy planning. Only two patients delivered at term, both received chemotherapy during pregnancy and had an elective cesarean section for maternal reasons.

Maternal outcome

All mothers with stage IV gastric cancer were deceased within 24 months after pregnancy, the majority within 6 months. Overall 1-year survival was 31%. The only patient in remission 12 months after diagnosis had stage II gastric cancer and was treated with chemotherapy during pregnancy followed by gastrectomy.

Outcome of the children

In total 10 pregnancies ended in a live birth. All six neonates prenatally exposed to chemotherapy were born without congenital malformations and all, except one with a birth weight 2950g and term delivery, were admitted to the neonatal intensive care unit (NICU), mostly for prematurity (4/5 or 80%). One infant born at term was admitted for neonatal abstinence syndrome due to maternal use of methadone. Two neonates prenatally exposed to chemotherapy, to 6 cycles FOLFOX and 3 cycles carboplatin/paclitaxel, respectively, (2/6 or 33%) were SGA at birth. The four non-exposed neonates were admitted to the NICU for prematurity and two of them where SGA (2/4 or 50%). The neonatal period of one child born at 32 weeks of gestation, two weeks after the last administration of carboplatin, was complicated by a bacillus cereus infection with a cerebral abscess. This was treated with antibiotics, however the neonate had residual cerebral palsy, epilepsy and hemianopia. Despite these symptoms requiring intensive physiotherapy, the child was doing well in

cognitive development at 15 months, 3 years and 6 years of follow-up according to standardized and clinically measures of neurocognitive functions. One child born at 34 weeks of gestational age was cognitively assessed at 18 months of age and had an appropriate cognitive development when corrected for his prematurity at birth. Available middle-long term follow-up of four children that are included in the INCIP study is shown in Table SII-II.5.1.

Results of narrative literature review

The largest review to date of 137 Japanese patients with pregnancy-associated gastric cancer was published in 2009; one third of patients with reported timing of delivery were diagnosed with gastric cancer postnatally.[245] The authors identified that 92.5% of the patients had advanced stage gastric cancer and the diffuse type was the most common histological diagnosis. Maternal outcome was poor with 1- and 2-year survival rate of 18.3% and 15.1%. A review of 31 cases (42% postpartum diagnosis) from western academic journals between 1969 and 1999 and a case series of 65 Asian patients (35% postpartum diagnosis) published in 2014 had similar findings.[249,250]

In the literature we identified five patients receiving a 5-FU-based regimen for advanced gastric cancer during pregnancy, with re-assuring fetal outcomes.[252-254] Details are summarized in Table SII-II.5.2. One patient received paclitaxel and S1 (tegafur (=prodrug of active substance 5-FU), gimeracil, oteracil) and delivered a growth restricted baby at 34 weeks of gestation.[255] Nishie et al summarized three additional Japanese cases with re-assuring neonatal outcome after prenatal exposure to S1 and taxanes (cases not included as reported in Japanese language).[255]

Discussion

In this case series the obstetrical and maternal outcomes of 13 patients with a diagnosis of primary or recurrent gastric cancer during pregnancy are reported. Most patients were diagnosed at an advanced stage with a diffuse type adenocarcinoma, including eight patients with signet ring-cell carcinoma. Larger case series had similar findings, however none of these studies reported on the use of chemotherapy during pregnancy or neonatal outcome in detail and most included large percentage of patients diagnosed postnatally.[245,249,250]

5-year survival in young (≤40 years) patients is 47.6% in general, but is highly dependent tumor stage (range 83.3% for stage I and 0% for stage III and IV).[256] Young patients are reported to have lower overall survival compared to patients > 40 years of age if curative resection is not achieved.[256] Furthermore, in a retrospective analysis of clinic-pathological features and outcome of 4722 non-pregnant patients, female sex was significantly associated with a younger age at diagnosis, poorly differentiated adenocarcinoma and signet ring cell carcinoma. [257] Due to these features, overall survival was poorer for female than for male patients, especially among patients younger than 45 years of age with advanced disease. The histological features of the gastric cancer in pregnant patients are similar to those reported in non-pregnant female patients. Nevertheless, gastric cancer during pregnancy has a poor prognosis with reported median overall survival of 7 months and 3-year overall survival of 23.3%. 1-year overall survival in this series was 31% (4/13 alive 12 months after diagnosis).To evaluate the effect of pregnancy on gastric cancer, Lee et al. compared 15 pregnant patients to 53 age-matched non-pregnant patients.[247] During gestation, 93% of patients were diagnosed with advanced stage gastric cancer, 60% of tumors were unresectable and three-year survival rate was 23.3%. Significant differences between both groups were found regarding the tumor stage, but in multivariate analysis pregnancy was not found to be an independent risk factor. It is unknown if a delay in diagnosis due to pregnancy explained this difference in tumor stage. A more recent study that compared overall survival of 20 patients with pregnancy-associated gastric cancer with 39 age- and stage-matched non-pregnant females concluded that advanced stage and tumor location but not pregnancy status are poor prognostic factors.[258]

Estrogen receptors (ER) are found in about 20-30% of human gastric cancers, mainly in the poorly differentiated type.[249] A recent meta-analysis suggested that the tumoral expression of ERα might indicate poor survival and the absence of ERβ is associated with lymph node metastasis.[259] However, the clinical significance of ER and (if there is) estrogen-dependent tumor growth in gastric cancer is still unclear.

There is no evidence of severe adverse neonatal outcome or increased risk of congenital malformations if regimens are administered after fetal organogenesis (occurring 2 to 8 weeks after conception) while avoiding preterm delivery.[40,100] The degree of placental transfer of drugs depends on molecular weight, lipophilicity, ionization at physiological pH and plasma protein binding, besides drug dose and gestational age at exposure. Also interaction with active drug transporters, like p-glycoprotein and BCRP (Breast Cancer Resistance Protein)

might affect the transfer rate. Pre-clinical data and limited clinical data of individual drugs used in the treatment of gastric cancer during pregnancy are summarized in Table 2. [40,48-50,80,84,260-264] Albeit, in clinical practice, most chemotherapeutic agents are given in combination regimens with co-medication, which might also influence the placental transfer by drug interactions.

Table 2: Pre-clinical and clinical data on placental transfer for most common cytotoxic drugs used for gastric cancer

Drug	Drug characteristics[Δ]	Pre-clinical data (placental transfer)	Ref.	Clinical data	Reference
5-FU (Fluorouracil)	MW*: 130 g/mol Negligible PB (8-12%)	28% *(rat model)*	Boike et al [50]	Large case series on use of anthracycline-based chemotherapy (including FEC and FAC) during pregnancy in breast cancer patients; use during second and third trimester of pregnancy seems relatively safe.	Amant et al. [40] Cardonick et al. [80]
Capecitabine (prodrug of 5-FU)	MW*: 359 g/mol Limited PB (<60%)	No data		One case report, colorectal cancer, treated in first trimester; no congenital malformations	Cardonick et al. [80]
Platina					
Oxaliplatin	MW*: 397 g/mol High PB (>90%)	No data	Al-Saleh et al [260]	Few case reports on oxaliplatin (one case of neonatal hypothyroidism in 8 patients treated with FOLFOX for colorectal cancer)	Pellino et al. [262]
Cisplatin	MW*: 298 g/mol, High PB (>90%)	2-24% *(ex vivo placental perfusion model)*	Van Calsteren et al. [49]		Amant et al. [40]
Carboplatin	MW*: 371 g/mol Limited PB (25-40%)	up to 57% *(baboon model)*		Reports of hearing loss when cisplatin used during pregnancy. Carboplatin appears to be a safer alternative.	
Epirubicin	MW*: 543 g/mol Moderate PB (~77%)	Less than 10% *(baboon model)*	Van Calsteren et al. [48]	Large case series on use of anthracycline-based chemotherapy during pregnancy in breast cancer patients; use during second and third trimester of pregnancy seems relatively safe.	Amant et al. [40] Cardonick et al. [80]
Taxanes					
Paclitaxel	MW*: 854 g/mol High PB (89-98%)	Low (<2%, paclitaxel) or undetectable (docetaxel) in fetal plasma, however accumulation in fetal tissue (metabolisation of taxanes still immature) *(baboon model)* Paclitaxel modulates expression of placental drug transporters of anticancer agents *(ex vivo placental perfusion model)*	Van Calsteren et al. [49] Berveiller et al. [261]	Favorable toxicity profile in small case series when administered during second or third trimester of pregnancy (12-25 patients)	Cardonick et al [84]
Docetaxel	MW*: 808 g/mol High PB (94-97%) *Drug efflux by placental p-glycoprotein transporter*				
Trastuzumab	IgG monoclonal antibody MW*: 145531 g/mol	Placental transfer by specific receptor-mediated active transport (not active in early pregnancy), up to 85% *(baboon model)*	Van Calsteren et al. [49]	Risk of oligohydramnios, hypoplastic lungs and fetal death by its ligation to HER2-receptors that are present in the renal epithelium of the fetus Exclusive exposure during first trimester of pregnancy appears not to be associated with abnormalities (HERA trial)	Azim et al. [263]

[Δ]Reference for drug characteristics: Drugbank 5.0 [29]
*Agents with low molecular weight (<500 g/mol) and low protein binding will easily cross the placenta
MW: molecular weight; PB: protein binding; HER2: Human epidermal growth factor receptor 2; HERA: Herceptin Adjuvant Trial; 5-FU: 5-Fluorouracil; FOLFOX: 5-FU and oxaliplatin; FEC: 5-FU, epirubicin, cyclophosphamide; FAC: 5-FU, Adriamycin (doxorubicin), cyclophosphamide

Most pregnant patients presented with extensive intra-abdominal disease that theoretically might provoke spontaneous preterm contractions. Interestingly all preterm deliveries, except one, were iatrogenic for oncological or obstetrical reasons. Four out of 10 infants were small for gestational age and this is of special interest as perinatal morbidity and mortality and cardiovascular and metabolic diseases, are more frequently seen in SGA children than in children of average weight (according to gestational age) at birth.[265] SGA in this population might be explained by the poor maternal general and nutritional status inherent to gastric cancer.

In addition, two of these children were prenatally exposed to chemotherapy, which is also reported to be associated with SGA.[100] In this series three patients developed pre-eclampsia, possibly explained by the relatively high maternal age (diagnoses at the age of 27, 37 and 39 for three cases respectively).

Current recommendations for the management of pregnant patients with a diagnosis of gastric cancer is based on available case series.[245,247,249] Treatment options depend on gestational age and cancer stage. If possible, the best oncologic management for the mother should be aimed for. An individualized management plan is required, always taking patient's perspective into account. In case of primary resectable disease, curative treatment should be aimed for with or without perioperative chemotherapy, depending on stage. Depending of the surgeon's expertise and gestational age, a laparoscopic approach is feasible. In late pregnancy, preterm delivery can be considered as the gravid uterus and maternal general condition can complicate surgery, however for optimal fetal outcome term delivery should always aimed for if possible. When perioperative chemotherapy is indicated, cytotoxic agents may be administered during pregnancy (from the second trimester onwards) in order not to delay treatment and enhance fetal maturity. In patients diagnosed with advanced stages of disease, where no cure is possible, immediate onset of systemic (palliative) treatment might be indicated to treat symptoms and to enhance fetal maturity if there is a wish to continue pregnancy. In early pregnancy and especially in advanced cases termination of pregnancy also can be considered. Available case reports on chemotherapy during pregnancy for gastric and colorectal cancer suggest that 5-FU based regimens (i.e. FOLFOX) are feasible.[252-255,262] In general, the use of cytotoxic drugs can only be justified if the risks of both mother and child are balanced and the benefits for maternal outcome outweigh the possible adverse effects on the child. Studies on the short-term neurocognitive development of children reveal that preterm delivery rather than prenatal exposure to cancer treatment is responsible for impaired cognitive outcome.[40] However, long-term outcome of children prenatally exposed to chemotherapy still remains under investigation and further follow-up of these children is indispensable.

Although this series on Western patients is small, we report on the use of chemotherapy for gastric cancer during pregnancy and the neonatal outcome in detail including follow-up. Continuous prospective registration of cases will facilitate future patient counselling. International collaboration is welcomed in order to collect data in larger numbers to improve treatment approach during pregnancy.

Conclusion

In summary, gastric cancer during pregnancy is a rare diagnosis. Patients present usually in advanced stage and have a poor prognosis. Early recognition of symptoms is indispensable for diagnosis in curative stage. In pregnant patients with persistent gastro-intestinal symptoms that cannot be explained by pregnancy only there should be a low threshold for further diagnostic procedures. While balancing maternal and fetal risks, the initiation of chemotherapy during pregnancy may be considered in order to reach fetal maturity.

Chapter III - Association of Chemotherapy Timing in Pregnancy with Congenital Malformation: results from the International Network on Cancer, Infertility and Pregnancy

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Abstract

Importance: Chemotherapy during the first trimester of pregnancy should be avoided owing to the risk of congenital anomalies. However, the precise gestational age at which chemotherapy can be initiated safely remains unclear.

Objective: To assess congenital anomaly rates associated with gestational age at initiation of chemotherapy among pregnant women with cancer.

Design, setting and participants: This multicenter cohort study evaluated all pregnant women who received chemotherapy between 1977 and 2019 registered in the International Network on Cancer, Infertility and Pregnancy (INCIP) database. Data were analyzed from February 15 to June 2, 2020.

Exposures: Cancer treatment with chemotherapy during pregnancy.

Main outcomes and measures: Analysis was focused on major and minor structural anomalies in offspring, defined by EUROCAT, detected during pregnancy or at birth.

Results: A total of 755 women in the INCIP database who underwent cancer treatment with chemotherapy during pregnancy were included in analysis. The median (range) age at cancer diagnosis was 33 (14-48) years. Among offspring, the major congenital anomaly rate was 3.6% (95% CI 2.4%-5.2%), and the minor congenital anomaly rate was 1.9% (95% CI 1.0%-3.1%). Chemotherapy exposure prior to 12 weeks gestational age was associated with a high rate of major congenital malformations, at 21.7% (95% CI, 7.5-43.7%; odds ratio, 9.24 [95% CI, 3.13-27.30]). When chemotherapy was initiated after gestational age 12 weeks, the frequency of major congenital malformations was 3.0% (95% CI 1.9%-4.6%), which was similar to the expected rates in the general population. Minor malformations were comparable when exposure occurred before or after gestational age 12 weeks (4.3% [95% CI 0.1%-21.9%] vs 1.8% [95% CI 1.0-3.0]; odds ratio 3.13 (95% CI 0.39-25.28). Of 29 women who received chemotherapy prior to 12 weeks gestation, 17 (58.6%) were not aware of pregnancy, and 6 (20.7%) experienced a miscarriage (3 women [10.3%]) or decided to terminate their pregnancy (3 women [10.3%]).

Conclusions and relevance: This cohort study found that chemotherapy was not associated with an increased risk of major congenital anomalies. The risk of congenital anomalies when chemotherapy was administered during the first trimester and the high number of incidental pregnancies during cancer treatment in the INCIP registry underscore the importance of contraceptive advice and pregnancy testing at the start of chemotherapeutic treatment in young women with cancer.

Introduction

Because chemotherapy attacks rapidly proliferating cells and is minimally selective, it also puts a developing fetus at risk of teratogenic effects. Toxic events during the periconceptional period might affect early embryogenesis and result in a miscarriage, whereas subsequent toxic exposure might interfere with the formation of organs, with the most susceptible period occurring between 2 and 8 weeks after conception (between 4 and 10 weeks post-menstruation).[39] There is a wide consensus that chemotherapy should be administered until after organogenesis is completed, usually considered the first trimester of pregnancy (ie, the first 13 weeks postmenstruation).[39,57] However, the exact timing of conception might be uncertain, and some systems (eg, eyes, genitals, hematopoietic system, central nervous system) continue to develop after 10 weeks of gestation. Therefore, the question remains in clinical practice: at what exact gestational age can chemotherapy be safely initiated to avoid inducing congenital anomalies?

To assess the immediate teratogenic role of prenatal chemotherapy, this cohort study evaluated the presence of major and minor congenital anomalies detected during pregnancy or at birth among the offspring of patients registered in the International Network of Cancer, Infertility and Pregnancy (INCIP).

Methods

The Ethical Committee of Unity Hospitals of Leuven, Belgium approved data collection for this cohort study. Prospectively registered patients provided written informed consents. Retrospectively registered patients were deidentified, so the need for informed consent was waived. The study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guidelines for cohort studies.

The INCIP contains retrospectively and prospectively collected oncological, obstetric, and neonatal data, as well as offspring follow-up data of patients diagnosed with any pregnancy-associated malignant neoplasm, reported by physicians with a special interest in cancer in young women. Currently, there are 73 hospitals in 28 countries actively participating in INCIP. The registry was started in 2005, and this cohort study was performed with a data cutoff of December 1, 2019. Patient data, including gestational age at treatment initiation, duration of chemotherapy during pregnancy, and obstetric and neonatal outcomes, were collected for all pregnant women who received chemotherapy with known obstetric outcomes. Small for gestational age (SGA) was defined as a birthweight less than the 10th percentile, and percentiles were corrected for gestational age, sex, maternal height, maternal weight, ethnicity, and parity, according to the calculator from the Gestation Network (version 8.0.4; Perinatal Institute). Preterm delivery was defined as birth before 37 weeks gestational age. Congenital anomalies were

Table 1: Clinical characteristics of patients

Characteristics	Patients, No. (%)		
		Gestational age at chemotherapy exposure	
	Total (N = 755)	< 12 wk (n = 29)	Exposure ≥ 12 weeks of gestation (n=726)
Maternal age at cancer diagnosis, y			
Median IQR [range]	33 (30-36) [14-48]	32 (29-35) [19-41]	33 (30-36) [14-48]
<30	175 (23.2)	9 (31.0)	116 (22.9)
30-35	344 (45.6)	15 (51.7)	328 (45.2)
>35	236 (31.3)	5 (17.2)	231 (31.8)
Cancer type			
Breast	451 (59.7)	17 (58.6)	434 (59.8)
Cervical	59 (7.8)	0	59 (8.1)
Lymphoma	138 (18.3)	4 (13.8)	134 (18.5)
Leukemia	36 (4.8)	7 (24.1)	29 (4.0)
Ovarian Cancer	26 (3.4)	0	26 (3.6)
Gastrointestinal Cancer	27 (3.6)	0	27 (3.7)
Melanoma	1 (0.1)	0	1 (0.1)
Brain	3 (0.4)	1 (3.4)	2 (0.3)
Lung	4 (0.5)	0	4 (0.6)
Sarcoma	5 (0.7)	0	5 (0.7)
Other	5 (0.7)	0	5 (0.7)
Country of registration			
Belgium	146 (19.3)	4 (13.8)	142 (19.5)
Czech Republic	28 (3.7)	0	28 (3.9)
Germany	7 (0.9)	0	7 (1)
Denmark	9 (1.2)	1 (3.4)	8 (1.1)
Spain	5 (0.7)	0	5 (0.7)
Italy	82 (10.9)	0	82 (11.3)
Mexico	19 (2.5)	2 (6.9)	17 (2.3)
The Netherlands	162 (21.5)	9 (31.0)	153 (21.1)
Russia	67 (8.9)	3 (10.3)	64 (8.8)
USA	197 (26.1)	9 (31.0)	188 (25.9)
Israel	7 (0.9)	0	7 (1.0)
Other	26 (3.4)	1 (3.4)	25 (3.4)
Timing of cancer diagnosis			
Before pregnancy	14 (1.9)	7 (24.1)	7 (1.0)
First trimester	217 (28.7)	22 (75.9)	195 (26.9)
Second trimester	448 (59.3)	0	448 (61.7)
Third trimester	76 (10.1)	0	76 (10.5)
Pregnancy known at time of chemotherapy initiation			
No	23 (3.0)	17 (58.6)	6 (0.8)
Yes	732 (97.0)	12 (41.4)	720 (99.2)
Conception			
Spontaneous	689 (92.5)	25 (86.2)	673 (92.7)
ART	57 (7.5)	4 (13.8)	53 (7.3)
Prior Pregnancies			
No	291 (38.5)	10 (34.5)	281 (38.7)
Yes	439 (58.1)	16 (55.2)	423 (58.3)
Not reported	25 (3.3)	3 (10.3)	22 (3.0)
Radiation therapy (first trimester)	18 (2.4)	1 (3.4)	17 (2.3)
Surgery (first trimester)	315 (41.7)	12 (41.4)	303 (41.7)

defined as structural or chromosomal anomalies that were diagnosed prenatally or at birth. Classification in minor or major anomalies was performed based on the medical, functional or cosmetic consequences, according to EUROCAT guidelines.[266]

Statistical Analysis

We used descriptive analyses and observed the numbers of reported congenital malformations according to gestational age at first chemotherapy exposure. The subgroup that initiated chemotherapy before 12 weeks of pregnancy was reported separately, and we defined the odds ratio (OR) and 95% CI for congenital malformations prior to 12 weeks of gestation. The χ^2 test was used to compare occurrence of malformations between the group exposed to chemotherapy prior to 12 weeks and the group with exposure after 12 weeks. P values were 2-sided, and P <.05 was considered to indicate statistical significance for all analyses. Analyses were performed using SPSS Statistics version 25.0 (IBM). Data were analyzed from February 15 to June 2, 2020.

Chemotherapy regimen during pregnancy			
ABVD	73 (9.7)	1 (3.4)	72 (9.9)
Anthracyclines	320 (42.4)	5 (17.2)	315 (43.4)
Anthracyclines and taxanes	122 (16.2)	12 (41.4)	110 (15.2)
CHOP-like	53 (7.0)	3 (10.3)	50 (6.9)
Platinum-based	108 (14.3)	0	108 (14.9)
Methotrexate	1 (0.4)	1 (3.4)	0
Leukemia regimen	36 (4.8)	6 (20.7)	30 (4.1)
Temozolomide	3 (0.4)	1 (3.4)	2 (0.3)
Other	39 (5.2)	0	39 (5.4)
Gestational age at first chemotherapy exposure, wk			
Median (IQR) [range]	22.6 (17.9-27.1) [0-35.1]	8.5 (1.6-11.1) [0-11.7]	22.9 (18.4-27.3) [12.0-35.1]
0-3.9 weeks	10 (1.3)	10 (34.5)	0
4-9.9 weeks	9 (1.3)	9 (31.0)	0
10-13.9 weeks	42 (5.4)	10 (34.5)	32 (4.4)
14-27.9 weeks	535 (70.8)	0	535 (73.7)
28-40.0 weeks	159 (21.1)	0	159 (21.9)
Other medication during pregnancy			
G-CSF	77 (10.2)	8 (27.6)	69 (9.5)
Tamoxifen	2 (0.3)	2 (6.9)	0
Trastuzumab	3 (0.4)	0	3 (0.4)
Rituximab	41 (5.4)	0	41 (5.6)
Imatinib	1 (0.1)	0	1 (0.1)
GnRH analogue	1 (0.1)	1 (3.4)	0
Isotretinoine	1 (0.1)	1 (3.4)	0
Mercaptopurin	12 (1.6)	12 (41.4)	0
Pregnancy outcome			
Live birth	745 (98.7)	23 (79.3)	722 (99.4)
Stillbirth	4 (0.5)	0	4 (0.6)
Miscarriage	3 (0.4)	3 (10.3)	0
Termination	3 (0.4)	3 (10.3)	0
Singleton/multiple pregnancy			
Singleton	731 (96.8)	21 (72.4)	710 (97.8)
Multiple	18 (2.4)	2 (6.9)	16 (2.2)
Gestational age at delivery[a], wk			
Median (IQR) [range]	36.7 (34.9-38.1) [22.1-42.4]	37.3 (34.6-38.9) [29.4-40.6]	36.7 (34.9-38.0) [22.1-42.4]
<28 weeks	9 (1.2)	0	9 (1.2)
28.0-31.9 weeks	38 (5.1)	3 (13.0)	35 (4.8)
32.0-33.9 weeks	71 (9.5)	2 (8.7)	69 (9.6)
34.0-36.weeks	277 (37.2)	3 (13.0)	274 (38.0)
≥37.0 weeks	35(47.0)	15 (65.2)	335 (46.4)
Congenital anomalies (n=749)[b]			
None	708 (94.5)	17 (73.9)	691 (95.2)
Minor	14 (1.9)	1 (4.3)	13 (1.8)
Major	27 (3.6)	5 (21.7)	22 (3.0)

[a] Among 745 live births.

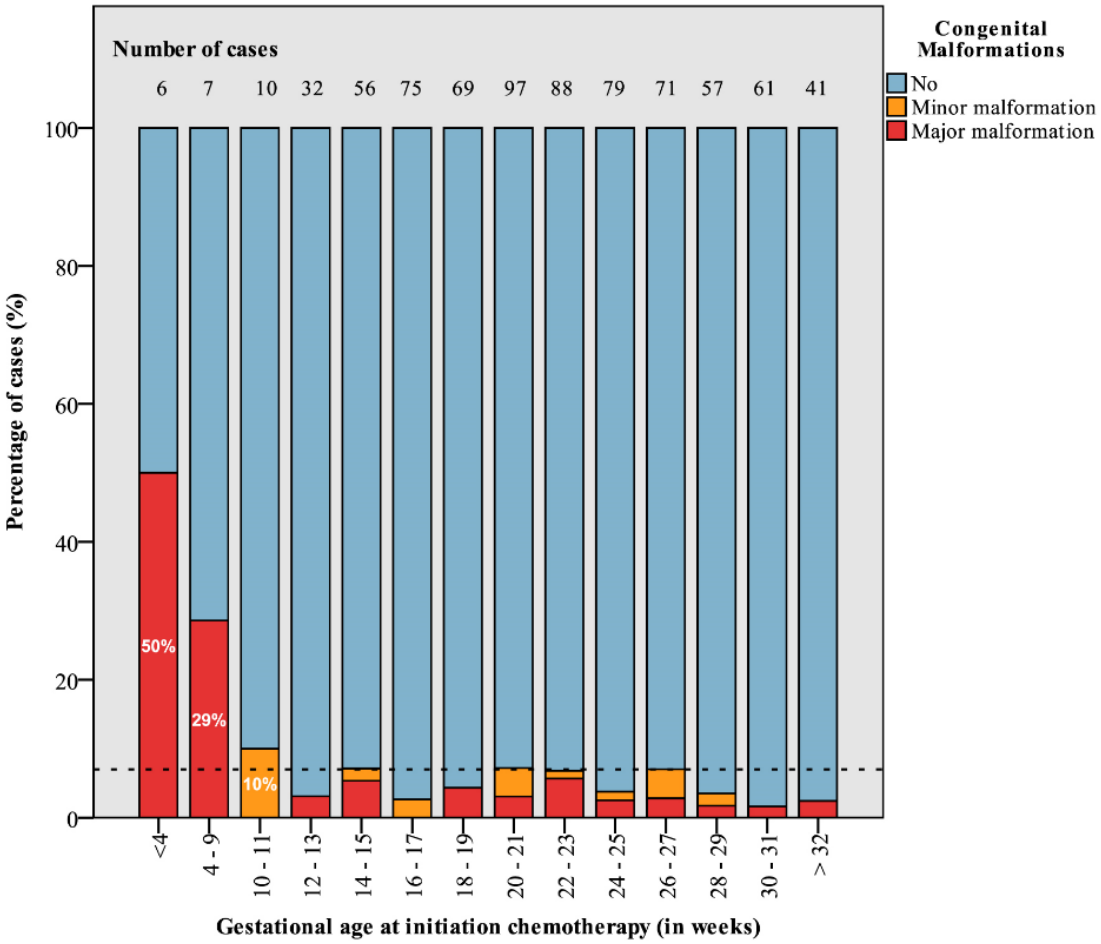
[b] Comparison between occurrence of minor and major anomalies between groups by Fisher exact: *P*<0.01 for major anomalies and *P*=.36 for minor anomalies

Abbreviations: ART: assisted reproductive technology; ABVD: doxorubicin, bleomycin, vinblastine, dacarbazine; CHOP: cyclophosphamide, doxorubicin, vincristine; CHOP: cyclophosphamide, doxorubicin, vincristine; G-CSF: Granulocyte colony-stimulating factor; dacarbazine; GnRH: gonadotropin-releasing hormone; IGR: Interquartile Range.

Results

In total, 755 pregnant women treated with chemotherapy between 1977 and 2019 were included in analysis (Table 1). Median (range) maternal age at cancer diagnosis was 33 (range 14-48) years. Breast cancer was the most common cancer type (451 women [59.8%]), and most pregnancies ended in a live birth (745 women, [99.4%]). A total of 27 neonates (3.6%, [95% CI, 2.4%-5.2%]) were reported to have major congenital anomalies, and 14 neonates (1.9% [95% CI, 1.0%-3.1%]) had minor congenital anomalies. The occurrence of major congenital anomalies was the highest if first chemotherapy exposure was prior to 12 weeks gestational age, at 21.7% (95% CI, 7.5%-43.7%), compared with 3.0% (95% CI, 1.9%-4.6%) congenital anomalies among offspring of women who began chemotherapy after 12 weeks gestation (OR 9.24 [95% CI, 3.13-27.30]), with the greatest risk for women who began chemotherapy periconceptionally (Figure and Table 2). The occurrence of major anomalies when chemotherapy was initiated after 12 weeks of gestation was lower and remained stable with advanced pregnancy (Figure). The occurrence of minor anomalies was comparable with the rates expected in the general population when exposure occurred prior or after 12 weeks gestational age (4.3% [95% CI, 0.1%-21.9%] vs 1.8% [95% CI, 1.0-3.0]; OR 3.13 [95% CI, 0.39-25.28]).

Figure 1: Frequency of congenital anomalies according to gestational age at first chemotherapy exposure.
The dotted line indicates 7%, the maximum percentage of congenital anomalies (both minor and major) according to gestational age at initiation of chemotherapy, from 12 weeks onwards



A total of 29 women initiated chemotherapy prior to 12 weeks of gestation. In 17 women (58.6%), pregnancy status was not known at the moment of chemotherapy initiation. A total of 6 patients (20.7%, all with hematological malignant neoplasms) experienced an early miscarriage after chemotherapy (3 women [10.3%]) or opted to terminate the pregnancy for oncological reasons (3 women [10.3%]). Of the remaining 23 neonates prenatally exposed to chemotherapy prior to 12 weeks of gestation, 6 (26.1%) had congenital anomalies (Table 2, Figure SII-IV.1). Notably, 2 children presented with very similar symmetrical limb deformations following exposure to anthracycline-based treatment (ie, docetaxel, doxorubicin; cyclophosphamide and 5-flourouracil, epirubicin, cyclophosphamide).

Table 2: Overview of pregnancy outcomes in women with chemotherapy exposure prior to 12 weeks of gestation

Pregnancy outcome	No. (n = 29)	Chemotherapy regimen	Congenital anomaly
Initiation at <4 wk GA (n = 10)			
Miscarriage	2	NR	NA
Termination	2	Polychemotherapy (n =1) for AML	NA
		MTX (n = 1) for AML	
Live birth, no anomalies	3	CHOP (n = 1)	NA
		Temozolomide (n = 1)	
		MTX (n = 1)	
Live birth, with anomalies	3	Temozolomide (n = 1)	Microcephaly[a]
		TAC (G-CSF) (n = 1)	Limb abnormalities (bilateral III-IV syndactyly of hands and feet, and a hypoplasia of the right thumb)[a]
		TAC (tamoxifen + G-CSF + RT breast) (n = 1)	VSD and unilateral kidney agenesia[a]
Initiation at 4-9 wk GA (n = 9)			
Miscarriage	1	Polychemotherapy (n =1) for AML	NA
Termination	1	Polychemotherapy (n =1) for CLL	NA
Live birth, no anomalies	5	Ara-C (n = 1)	NA
		FEC (n = 1)	
		AC (n = 3)	
Live birth, with anomalies	2	CHOP (n = 1)	Epstein anomaly and dextrocardia[a]
		FEC (tamoxifen + GnRH agonist) (n = 1)	Limb abnormalities[a]
Initiation at 10-11 wk GA (n = 10)			
Miscarriage	0	NA	NA
Termination	0	NA	NA
Live birth, no anomalies	9	ABVD (n =1)	NA
		AC (n = 5)	
		AC (G-CSF) (n = 1)	
		EC (G-CSF) (n = 2)	
Live birth, with anomalies	1	AC (n = 1)	Plagiocephaly

[a] Major congenital anomaly according to EUROCAT

Abbreviations: ABVD: doxorubicin, bleomycin, vinblastine, dacarbazine; AC: doxorubicin, cyclophosphamide; AML: Acute myeloid leukemia; Ara-C: cytarabine; CHOP: cyclophosphamide, doxorubicin, vincristine; CLL: chronic lymphocytic leukemia; EC: epirubicin; F: 5-flourouracil, cyclophosphamide; GA: Gestational Age; G-CSF: Granulocyte colony-stimulating factor; GnRH: Gonadotropin-releasing hormone; MTX: Methotrexate; NA: not applicable; NHL: Non-Hodgkin lymphoma; NR: not reported; R: rituximab; RT: Radiation Therapy; TAC: doxorubicin, cyclophosphamide, docetaxel; VSD: Ventricular Sepal Defect.

Discussion

This cohort study presents the largest and most detailed cohort on congenital anomaly occurrence according to gestational age at chemotherapy exposure, to our knowledge. We found an association between chemotherapy before 12 weeks of gestation and increased risk of congenital anomalies detected during pregnancy or at birth. The overall congenital anomaly rate among offspring of mothers who initiated chemotherapy after 12 weeks of gestation was 4.8%, which is comparable to the expected rates in the general population (ie, 2.5%-6.9% for major anomalies and 6.5-35.8% for minor anomalies).[267-269] Furthermore, 23 patients (3.0%) received chemotherapy without awareness of the pregnancy, underscoring the importance of adequate anticonception counseling and pregnancy testing at the start of chemotherapeutic treatment in young women with cancer.

To date, questions remain regarding when in the gestational period chemotherapy can be initiated relatively safely. First-trimester chemotherapy exposure has been associated with 10% to 20% risk of major malformations.[39] Mechanisms by which chemotherapeutics induce teratogenic effects are incompletely understood. To date, the reported anomalies after oncological treatment during human pregnancy encompass all organ systems, without discernible pattern for most cytotoxic drugs, except for aminopterin and

methotrexate.[39] The nature of teratogenesis is extremely complex; individual genetic susceptibility, specific timing of cytotoxic exposure, and specific type of (co-)medication all determine the spectrum of anomalies. Similar to the findings reported in this study, other studies have reported limb deformities after exposure to a combination of cyclophosphamide and 5-fluorouracil in the first trimester of pregnancy.[270,271] Most likely, this reflects chemotherapy-related toxic effects in the time frame when digits develop (ie, 5 to 6 weeks of gestation). However, proof of teratogenicity remains difficult because of other confounders, such as multidrug use, maternal age, and genetic predisposition.

We focused on structural anomalies detected prenatally or at birth. Adverse effects and anomalies can become apparent after birth as the eyes, genitalia, hematopoietic, and central nervous system continue to develop during childhood.[39] Nevertheless, after birth, other confounders (eg, infections, medication use, environmental factors) play a role. A cohort study on 225 pregnant patients receiving chemotherapy after 12 weeks of pregnancy focused on structural birth anomalies diagnosed up to 5 years after birth and revealed an increased risk when chemotherapy was administered between 12 and 17 weeks of gestation.[272] The causality of chemotherapy was unclear, as reported malformations were very heterogeneous (eg, pyloric stenosis, plagiocephaly, spina bifida) and could be also explained by other factors (eg, genetics, prematurity, folate deficiency). Functional anomalies, sometimes subtle, might appear in early childhood or later. Among pediatric patients who were directly exposed to chemotherapy, anthracyclines are notorious for cardiotoxic effects, whereas platinum derivatives are associated with early ototoxicity.[273,274] Another concern is the evolution of neurocognitive functions in the long term, since the central nervous system continues to develop during the second and third trimester of pregnancy. Postnatal exposure to chemotherapeutics has been associated with long-term genotoxic effects, such as a secondary malignant neoplasm and premature aging.[275,276] To date, cohort studies on children exposed to chemotherapy prenatally report overall reassuring results, mostly based on general health, cardiac evaluation, and cognitive development until the age of 6 years.[40] Additionally, these clinical studies did not report on genotoxic effects after prenatal chemotherapy. Since the administration of chemotherapy in cancer treatment concerns combinatorial regimens of multiple chemotherapeutic agents and could differ per patient or hospital, reported results cannot provide information about the safety or risks of individual chemotherapeutic agents. Therefore, more research regarding genetic damage and developmental aspects with subsequent long-term follow-up is planned. Data on the risks of congenital malformations are indispensable for clinicians and patients when considering chemotherapy during pregnancy.

Based on our findings, we suggest that when cancer is diagnosed in early pregnancy, chemotherapy can be initiated from 12 weeks onwards. Therefore, accurate ultrasonographic dating is crucial. The introduction of a 1-week safety period could be considered to further minimize the risk of chemotherapy-induced congenital anomalies. However, no rationale exists to delay the start of chemotherapy beyond 14 weeks of gestation, as

recommended previously.[57] If a patient desires certainty on risk of chromosomal anomalies, an amniocentesis for karyotyping and microarray could be offered, since noninvasive prenatal testing is not conclusive in patients with cancer owing to tumor cell-free DNA interference.[277]

Limitations

This study has some limitations. One important limitation of the INCIP cohort is that it is prone to selection bias, and data cannot be interpreted as population-based incidences. Based on this study, the absolute occurrence of anomalies after chemotherapy was impossible to assess, and minor anomalies are likely underreported. Additionally, early miscarriages and terminations of pregnancy are likely to be underrepresented in the INCIP registry, and with the substantial evolution of ultrasonograhic imaging and improved prenatal diagnosis of congenital anomalies over the years, more pregnancies might have been terminated. Furthermore, the use of multiple medications and treatment regimens in cancer treatment complicates the interpretation of results.

Conclusion

These findings suggest that chemotherapy during the first 12 weeks of pregnancy was associated with increased risk for congenital anomalies in the fetus. If an aggressive cancer diagnosis during early pregnancy does not allow treatment delay, parents should be counselled on fetal risks of malformations. If a patient incidentally becomes pregnant while receiving chemotherapy, prenatal counselling should include the risks of both short- and long-term adverse outcomes. Adequate anticonception and routine pregnancy tests should be offered to fertile women with cancer.

Chapter IV. - Obstetric and neonatal outcomes following oncological surgery during pregnancy : a multicenter retrospective cohort study of 643 patients

Abstract

Objective

This analysis aims to investigate the safety of oncological surgery during pregnancy and focuses on the obstetric and neonatal outcomes following extra-abdominal, abdominal and cervical surgery during pregnancy.

Methods

Data on the oncological treatment modalities, obstetric and neonatal outcomes were collected from the INCIP registry. We separated our cohort into three groups according to the type of surgery: extra-abdominal surgery, abdominal surgery and cervical surgery. We used a logistic regression model to compare obstetric and neonatal outcomes between the different types of surgical procedures.

Results

In total, 845 patients were eligible for analysis. Chemotherapy was given during pregnancy in 409 (48%) patients. Extra-abdominal surgery was performed in 664 patients (79%), of which 483 (73%) had breast surgery, 64 (10%) skin cancer surgery, 42 (6%) thyroid surgery and 20 (3%) neurosurgery. Abdominal surgery was done in 151 patients (18%); 116 of them (77%) were operated by laparotomy and 35 (23%) by a laparoscopic approach. Cervical surgery was performed in 30 patients (5.6%). Our data revealed no significant differences between the different types of surgery with respect to preterm spontaneous labor, preterm delivery and small for gestational age. Surgery during the third trimester appeared to be related with a higher risk of preterm delivery, compared to surgery during the first or second trimester of pregnancy (OR = 1.530, 95%CI(1.016;2.303), p = 0.0416).

Conclusion

The risk of preterm labor, preterm delivery and small for gestational age did not differ between extra-abdominal, abdominal and cervical surgery.

Introduction

Overall, 0.75% to 2% of pregnancies, are complicated by the need for surgical procedures.[278] Data indicate that surgery does not increase the risk of congenital malformations in the offspring nor the risk of maternal death.[279,280] However, the risk of miscarriage appears to be elevated, especially if surgery is performed during the first trimester .[242] Surgery might also increase the likelihood of preterm delivery and low birth weight.[281] Whereas extra-abdominal surgery is considered feasible and safe during pregnancy, abdominal and pelvic surgery is more complicated as the uterus enlarges .[282,283] Most common indications for abdominal surgery during pregnancy are limited to cholecystitis, appendicitis and ovarian cysts. Consequently, evidence is mostly based on outcomes following surgical intervention of these benign diseases. In comparison with laparotomy, low grade evidence suggests that laparoscopic surgery might be associated with a higher risk of fetal loss and thethe safety of laparoscopic surgery during pregnancy remains controversial .[284-287] Regarding preterm delivery, there was no significant difference between laparoscopy and laparotomy. [284,286,287].

To date, data about the safety of oncological surgery during pregnancy are limited to case reports and expert opinions. In order to improve insights and therapeutic approaches, a multicenter cohort study was conducted. This study aims to investigate the obstetric and neonatal outcomes following extra-abdominal, abdominal and cervical surgery during pregnancy of pregnant women with cancer registered by the International Network on Cancer, Infertility and Pregnancy (INCIP).

Methods

Study population and design

This observational retrospective cohort study obtained data of pregnant women with cancer from the INCIP registry. We identified 769 registered patients who had surgery during pregnancy. Patients with pre-invasive cancer, postpartum diagnosis, or missing essential data on the oncological treatment and pregnancy outcomes were excluded. In total, 643 patients diagnosed between 23 March 1961 and 04 March 2019 with borderline ovarian tumors or primary invasive cancer during pregnancy were included in the analysis. We separated our cohort into three groups according to the type of surgery: extra-abdominal surgery, abdominal surgery and cervical surgery. Outcomes of interest were preterm spontaneous labor [defined as preterm rupture of membranes (PPROM) or preterm contractions], preterm delivery, small for gestational age (SGA) neonates, admission to the neonatal intensive care unit (NICU), congenital malformations and pregnancy loss.

Procedures

Detailed data on the oncological treatment modalities, obstetric and neonatal outcomes were collected. All patients were diagnosed and staged according to local protocols, based on histopathological confirmation. PPROM was determined as preterm rupture of membranes without contractions. Preterm delivery was defined as birth before 37 weeks of pregnancy. Birth weight percentiles were calculated according to the calculator from the Gestational Network (www.gestation.net; GROW v8.0.2 2018).[177] Birth weight less than the 10th percentile was considered small for gestational age (SGA). Stillbirth was defined as a fetal death at or after 20 weeks of gestation, or a weight greater than or equal to 350 grams if the gestational age is not known.[288] Pregnancy loss before 20 weeks of gestational age was referred to as a miscarriage. Congenital malformations were determined according to the definitions of Eurocat.[148]

Statistical analysis

We conducted descriptive statistics to analyze oncological, obstetric, and neonatal data. A logistic regression model was used to investigate the association between obstetric and neonatal outcomes (PPROM or preterm contraction, preterm delivery, SGA, pregnancy loss, NICU admission) and type and timing of operation. Analyses were corrected for chemotherapy, as this was a major confounder for the assessed outcomes. Missing values in both outcomes and predictor variables were dealt with by means of multiple imputation. Ten imputation data sets were constructed by fully conditional specification (FCS). Analyses were performed on each completed data set and combined into unique summary statistics accounting for uncertainty due to the imputations. For obstetric outcomes (preterm spontaneous labor and preterm delivery) analysis was based on all singleton ongoing pregnancies, lasting more than 20 weeks of gestation. For neonatal outcomes (SGA, NICU admission and congenital malformations), we analyzed all singleton livebirths. Regarding pregnancy loss, the regression analysis was based on spontaneous miscarriages and stillbirths, excluding terminations of pregnancy. We emphasize the absence of a control group containing patients without cancer, resulting in a comparison limited to patients with cancer during pregnancy. Extra-abdominal surgery during pregnancy was used as a reference to compare outcomes following abdominal or uterine surgery in pregnancy. P-values of 0.05 or less were considered significant. Odds ratio (OR) and their 95% CI were reported. Descriptive analysis was done with IBM SPSS Statistics (version 26). The Firth logistic regression was done with R (version 3.5.2).

Results

Baseline characteristics of 845 pregnant women who underwent oncological surgery are described in Table 1. At the time of diagnosis, the median maternal age was 33 years (IQR 7). Distribution of cancer types is illustrated by Figure 1. Most pregnancies ended in a livebirth (810, 96%). There were 12

Table 1: Patient characteristics (n=845)

	All patients (n = 845)
Age at diagnosis, years	
Median (IQR; range)	33 (7; 14-45)
Missing	13
Period of diagnosis, n(%)	
1996-2004	151 (18%)
2005-2009	214 (25%)
2010-2015	298 (35%)
2016-202	185 (22%)
Trimester of pregnancy of diagnosis	
Diagnosis before pregnancy	18 (2%)
<13 weeks	327 (40%)
13-24 weeks	315 (39%)
24-32 weeks	130 (16%)
>32 weeks	27 (3%)
Parity at diagnosis	
Nulliparous	322 (42%)
Multiparous	443 (58%)
Missing	80
Treatment during pregnancy	
Only Surgery	414 (49%)
Surgery and chemotherapy	393 (47%)
Surgery and radiotherapy	17 (2%)
Surgery, chemotherapy and radiotherapy	16 (2%)
Surgery and targeted/hormonal therapy	5 (1%)
Trimester of surgery	
First trimester	236 (29%)
Second trimester	445 (55%)
Third trimester	132 (16%)
Missing data	32
Pregnancy outcome	
Live birth	810 (96%)
Still birth	8 (1%)
Spontaneous miscarriage	12 (1%)
Termination of pregnancy	15 (2%)
Mode of delivery*	
Vaginal delivery	489 (64%)
Caesarean section	278 (36%)
Missing	26
Planned delivery (IOL or elective cs)*	460 (59%)
Neonatal outcome*	
Birthweight (gram)	
Median (IQR; range), in grams	2863 (799, 520-4690)
Missing	120
Adverse obstetric outcome**	
Preterm spontaneous labor	88 (11%)
Missing	35
Preterm delivery	
Delivery < 28 weeks	6 (<1%)
Delivery 28-31 weeks (< 32 weeks)	27 (4%)
Delivery 32-33 weeks (< 34 weeks)	42 (6%)
Delivery 34-36 weeks (< 37 weeks)	234 (31%)
Missing	51
Adverse neonatal outcome*	
SGA	175 (26%)
missing	120
Admission to neonatal unit	176 (26%)
Days of hospitalization	
Median (IQR; range)	8 (18; 1-120)
Missing	59
Congenital malformations	
Minor	23 (3%)
Major	12 (2%)
Missing	76

Data are shown in n (%) or median (IQR; range). IOL = Induction of labor. Elective cs = elective caesarean section. PPROM = preterm, premature rupture of membranes. SGA= Small for gestational age = birth weight centile < 10.
* All singleton livebirths (n = 793), ** All singleton ongoing pregnancies (n=802)

miscarriages (7 prior to 12 weeks of gestation and 5 between 12 and 19 weeks of gestation); seven miscarriages followed after abdominal surgery (six laparotomy, one laparoscopy), 5 after extra-abdominal surgery (four breast surgery, one neurosurgery). There were eight stillbirths (range 21-32 weeks; two abdominal surgery, three breast surgery, one neurosurgery, one excision of lymphoma, one excision of melanoma), of which four fetuses deceased within three weeks following surgery.

Extra-abdominal surgery was performed in 664 patients (79%), of which 483 (73%) had breast surgery, 64 (10%) skin cancer surgery, 42 (6%) thyroid surgery and 20 (3%) neurosurgery. Abdominal surgery was done in 151 patients (18%); 116 of them (77%) were operated by laparotomy and 35 (23%) by a laparoscopic approach. Cervical surgery was performed in 30 patients (5.6%): 23 (76%) were treated with cervical conization and 7 with vaginal trachelectomy (median gestational age 14 weeks range 13-17), of which 3 patients also underwent laparoscopic pelvic lymph node dissection (range 13-14 weeks).

Preterm spontaneous labor occurred in 88 (11%) of 802 ongoing singleton pregnancies. In total, 308 (41%) pregnancies resulted in preterm delivery, of which 234 (76%) were planned and 66 (24%) were spontaneous. Of the 793 singleton live births, 175 (26%) neonates were SGA. In total, 176 (26%) neonates were admitted in NICU, mostly for a hospital stay more than 7 days (127 (72%)) An overview of treatment characteristics, obstetric and neonatal outcomes per surgery type is shown in Table 2. Remarkably, there were only two out of 30 (7%) women who underwent cervical surgery during pregnancy had preterm spontaneous labor. The majority of women (17, 60%) delivered by planned elective cesarean section after 37 weeks of gestation.

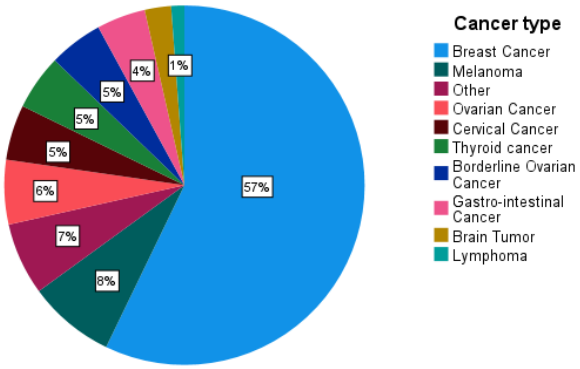


Figure 1: Distribution of cancer types treated with surgery during pregnancy (n=845)

There was no difference in the risk of preterm spontaneous labor, preterm delivery and small for gestational age in the different types of surgery (Table 3). The model provided support for a higher risk of preterm delivery when surgery was performed in the third trimester of pregnancy (OR = 1.530, 95%CI(1.016;2.303), $p = 0.0416$). Odds ratios were greater than 1 for preterm spontaneous labor, preterm spontaneous and preterm planned delivery, however did not reach significancy. Preterm delivery following surgery in third trimester of pregnancy is explained by both spontaneous, as well as planned preterm birth.

Table 2: Overview of treatment characteristics, obstetric and neonatal outcomes, stratified by surgical treatment modality.

	Extra-abdominal surgery (n = 664)	Abdominal surgery (n = 151)	Cervical surgery (n = 30)
Cancer type			
Breast cancer	483 (73%)	0 (0%)	0 (0%)
Melanoma	64 (10%)	2 (1%)	0 (0%)
Thyroid cancer	42 (6%)	0 (0%)	0 (0%)
Brain tumor	20 (3%)	0 (0%)	0 (0%)
Lymphoma	9 (1%)	1 (1%)	0 (0%)
Gastro-intestinal cancer	3[a] (1%)	34 (23%)	0 (0%)
Borderline ovarian tumor	0 (0%)	41 (27%)	0 (0%)
Invasive ovarian cancer	0 (0%)	49 (33%)	0 (0%)
Cervical cancer	0 (0%)	0 (0%)	0 (0%)
Other	46 (7%)	12 (8%)	30 (100%)
Period of surgery			
1996-2004	119 (18%)	25 (17%)	7 (23%)
2005-2009	166 (25%)	41 (27%)	7 (23%)
2010-2015	238 (36%)	49 (32%)	11 (37%)
2016-2021	141 (21%)	36 (24%)	5 (17%)
Maternal age at diagnosis (years), median (IQR; range)	34, 6, 19-45	31, 7, 17-42	32, 6, 27-43
GA at diagnosis (weeks), median (IQR, range)	15, 14, 0-37	15, 8, 2-29	14, 12, 3-37
Chemotherapy during pregnancy	358 (54%)	51 (34%)	3 (10%)
Radiotherapy during pregnancy	32 (5%)	2 (1%)	0 (0%)
Trimester of surgery			
First Trimester	186 (29%)	42 (28%)	8 (28%)
Second Trimester	325 (51%)	101 (68%)	19 (66%)
Third Trimester	124 (20%)	6 (4%)	2 (7%)
Missing	29	2	1

Pregnancy outcomes			
Live birth	643 (97%)	138 (91%)	29 (97%)
Still birth	6 (1%)	2 (1%)	0 (0%)
Miscarriage	5 (1%)	7 (5%)	0 (0%)
Termination of pregnancy	10 (2%)	4 (3%)	1 (3%)
GA at delivery/pregnancy termination (weeks), median (IQR; range)	37, 3, 25-42	38, 3, 28-41	38, 3, 34-41
All singleton ongoing pregnancies (n=802)	**N=636**	**N=137**	**N=29**
Preterm spontaneous labor*	76 (13%)	10 (8%)	2 (7%)
Preterm delivery*	258 (43%)	42 (32%)	8 (29%)
Planned	188 (32%)	38 (29%)	8 (29%)
Spontaneous	62(11%)	4 (3%)	0 (0%)
Gestational age at delivery			
<24 weeks	1 (<1%)	1 (<1%)	0 (0%)
24-27 weeks	3 (<1%)	1 (<1%)	0 (0%)
28-31 weeks	21 (4%)	6 (5%)	0 (0%)
32-33weeks	35 (6%)	7 (5%)	0 (0%)
34-36 weeks	198 (33%)	28 (22%)	8 (30%)
≥37 weeks	336 (57%)	87 (67%)	19 (70%)
Missing	42	7	2
All singleton livebirths (n=793)	**N=630**	**N=134**	**N=29**
SGA*	146 (26%)	31 (27%)	4 (17%)
Major Congenital malformations*	18 (3%)	3 (3%)	2 (8%)
NICU admission*	145 (27%)	27 (23%)	4 (17%)
Days of hospitalization, median (IQR; range)	7, (14; 1-120)	28, (42; 1-89)	5, (2; 4-6)

Data are shown in n (%) or median (IQR; range). IQR = interquartile range. GA = gestational age. SGA= Small for gestational age = birth weight centile < 10. NICU: Neonatal intensive care unit

*missing data were excluded (numbers not given) for calculation of percentiles

[a]Gastro-intestinal cancer with extra-abdominal surgery: 2 patients with endoscopic excision of rectal polyps at 15 and 29 weeks of gestation, respectively; 1 patient with oesophagal cancer underwent endoscopic resection at 22 weeks of gestation

Table 3: Multiple logistic regression of obstetric and neonatal complications (n=845)

	Pregnancy loss		**Preterm spontaneous labor**		**SGA**		**NICU admission**	
	OR(95% CI)	p	OR(95% CI)	p	OR(95% CI)	p	OR(95% CI)	p
Type of surgery**								
Extra-abdominal surg =ref.		0.079		0.572		0.631		0.677
Abdominal surg	2.199 (1.061;4.559)		0.688 (0.342;1.382)		1.254 (0.792;1.987)		0.962 (0.604;1.534)	
Uterine surg	0.607 (0.078;4.710)		0.864 (0.195;3.823)		0.870 (0.250;3.024)		0.609 (0.201;1.848)	
Surgery in third trimester of pregnancy (yes vs no)	0.159 (0.021;1.204)	0.075	1.665 (0.875;3.166)	0.120	0.947 (0.569;1.574)	0.832	1.793 (1.148;2.801)	0.010
	Preterm delivery <37weeks		**Elective preterm delivery <37 weeks**		**Spontaneous preterm delivery <37 weeks**		**Cesarean section**	
	OR(95% CI)	p	OR(95% CI)	p	OR(95% CI)	p	OR(95% CI)	p
Type of surgery**								
Extra-abdominal surg =ref.		0.288		0.993		0.095		0.003
Abdominal surg	0.737 (0.486;1.117)		1.015 (0.662;1.555)		0.349 (0.134;0.910)		0.975 (0.657;1.448)	
Uterine surg	0.715 (0.302;1.692)		1.046 (0.441;2.481)		-		3.897 (1.758;8.636)	
Surgery in third trimester of pregnancy (yes vs no)	1.530 (1.016;2.303)	0.042	1.372 (0.899;2.095)	0.1427	1.275 (0.585;2.780)	0.541	0.855 (0.559;1.306)	0.468

OR: odds ratio, CI: confidence interval; OR>(<)1: higher (lower) risk of adverse outcome for indicated category compared to reference. For all predictors analysis were corrected for the receipt of antenatal chemotherapy. For pregnancy loss: termination of pregnancy excluded) (n=830). For preterm spontaneous labor and preterm delivery: singleton ongoing pregnancies (n=802). For SGA and NICU (neonatal outcome): singleton live births only(n=793)

Discussion and conclusion

This multicenter retrospective study involving 845 patients who received oncological surgery during pregnancy, revealed no significant differences between the different types of surgery with respect to preterm spontaneous labor, preterm delivery and SGA. However, surgery during the third trimester appeared to be related with a higher risk of preterm delivery.

Literature indicated that the rates of preterm delivery following abdominal surgery ranged between 15-45%.[289] Overall, we observed a rate of 32%, which was equivalent to the literature findings. Data on laparoscopic interventions in this cohort were scarce, however reassuring. There have been recent advances in the surgical technique of abdominal surgery, shifting from an open to a laparoscopic approach. Laparoscopic surgery has been performed successfully in pregnancy for many benign conditions such as removal of the appendix, gallbladder or adnexal masses.[286,290] A recent study comparing 6018 patients who underwent laparoscopy versus laparotomy during pregnancy, revealed significantly less fetal adverse events and better operative and maternal outcomes after laparoscopic surgery.[291] However, the effect of pneumoperitoneum is a major consideration in relation to laparoscopic surgery. The infusion of gas carbon dioxide in the peritoneum is required to create space for surgical manipulation. Serious complications such as perforation of the uterus, hypercapnia and reduced blood flow due to the use of carbon dioxide and increased abdominal pressure have been reported. Nevertheless, as long as the recommendations of the maximal pressure (10-13 mmHg), operation time (90-120 min), open introduction and performance by an experienced surgeon are respected, this procedure is not considered hazardous to the fetus.[5] Data on miscarriage and preterm delivery following a laparoscopic procedure is contradictory. The meta-analysis and systematic review of Chakraborty et al. (20) suggested that laparoscopic appendectomy posed a higher risk of fetal loss, but a lower risk of preterm delivery.[285] Other studies refuted the conclusion of the reduced rate of preterm delivery but did observe a higher rate of fetal loss when the procedure was performed by laparoscopy.[292,293] In this cohort there was one miscarriage following laparoscopy and preterm delivery rate was 34% (11 out of 32).

Several surgical interventions have been described in early stage cervical carcinoma (IA1-IB2) during pregnancy.[5,294] If continuation of pregnancy is desired, possible treatment options are large conization, simple or radical trachylectomy. Significant complications have been reported related to cervical conization, such as hemorrhage (5-15%) spontaneous abortion (25%), premature labor/delivery and infection.[295] Vercellino et al. investigated 32 pregnant patients undergoing laparoscopic pelvic lymphadenectomy for cervical cancer. No adverse obstetric and neonatal outcomes were reported.[296] Our findings demonstrate that cervical surgery was not associated with a higher risk of pregnancy loss or preterm labor.

Although there is consensus in the surgical literature that surgical procedures are safe in all trimesters, surgery is usually delayed until after the first trimester when organogenesis is complete and the risk of miscarriage is

decreased.[5] The second trimester is thought to be the safest of all semesters with a lower anesthetic risk to the fetus, a lower risk of miscarriage and the additional benefit that the gravid uterus permits a certain degree of access to operate in the abdomen.[5,290] Buitrago and colleagues investigated 2507 women who underwent an appendectomy during pregnancy during the first, second and third trimester.[297] They observed a 1.6 times greater risk of preterm birth when surgery was performed during the third trimester. Our analysis showed a higher frequency of preterm delivery in patients who received surgery during the third trimester, compared to surgery during the first or second trimester of pregnancy, which could be caused by manipulation of the gravid uterus (spontaneous labor) or postoperative discomfort (planned delivery).

Limitations of this observational cohort include its retrospective nature, resulting in under-registration of complications and, inevitably, missing data. This cohort is not suitable to assess the risk of spontaneous miscarriage following oncological surgery, as no control group without surgery is included.

In conclusion, this multicenter retrospective cohort revealed no differences between extra-abdominal, abdominal and cervical oncological surgery with respect to preterm labor, preterm delivery and small for gestational age.

Chapter V. - Maternal and neonatal outcome after the use of G-CSF for cancer treatment during pregnancy

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Abstract

Data on the use of Granulocyte colony-stimulating factor (G-CSF) in pregnant cancer patients are scarce. The International Network of Cancer, Infertility and Pregnancy (INCIP) reviewed data of pregnant patients treated with chemotherapy and G-CSF, and their offspring. Among 2083 registered patients, 42 pregnant patients received G-CSF for the following indications: recent chemotherapy induced febrile neutropenia (5; 12%), dose dense chemotherapy (28, 67%), poly chemotherapy (7, 17%) or prevention of neutropenia at delivery (2; 5%). Among 24 women receiving dose dense chemotherapy, three (13%) patients recovered from asymptomatic neutropenia within 5 days. One patient developed pancytopenia following polychemotherapy after which the pregnancy was complicated by chorioamnionitis and intrauterine death. Nineteen singleton livebirths (49%) were born preterm. Sixteen neonates (41%) were admitted to the Neonatal Intensive care Unit (NICU). No neonatal neutropenia occurred. Two neonates had congenital malformations. Out of 21 children in follow-up, there were four children with a motor development delay and two premature infants had a delay in cognitive development. In conclusion, the rate of maternal and neonatal complications are similar to those described in (pregnant) women treated with chemotherapy. Due to small numbers and limited follow-up, rare or delayed effects among offspring exposed to G-CSF in utero cannot be ruled out yet.

Introduction

The co-occurrence of cancer and pregnancy, estimated to affect 1 in 1000 pregnancies, is expected to rise due to increasing maternal age and incidental findings at the occasion of the non-invasive prenatal testing (NIPT).[7,32] Breast cancer, melanoma, hematological and cervical cancer are the most common types of cancer diagnosed during pregnancy.[7,14] With the increasing awareness of the feasibility of antenatal cancer treatment, less pregnancies are terminated and more pregnant women receive chemotherapy.[100] Whenever possible, oncological treatment during pregnancy should adhere as much as possible to the standard of care treatment in non-pregnant patients, in order to safeguard prognosis.[4] However, consequences and safety of some supportive agents that are used as part of current standard therapy, such as Granulocyte Colony-Stimulating Factor (G-CSF), are still subject of discussion.

G-CSF supports the clonal growth of progenitors of neutrophils and regulates the proliferation and differentiation of hematopoietic stem cells. Both in vitro and in vivo studies confirmed transplacental passage of this glycoprotein[298,299] In oncological care, it is used to treat or prevent prolonged grade 3 [absolute neutrophil count (ANC) <1.0 x 109 /L] and 4 (ANC< 0.5 x 109/L) neutropenia or febrile neutropenia (grade 3-4 neutropenia with fever) in patients receiving chemotherapy.[300,301] In patients with high risk breast cancer, dose dense chemotherapy regimens with G-CSF support, are considered standard of care.[4,302]

As available data are still limited to case reports and small case series, use of antenatal G-CSF is still debated.[303,304] Hence, more maternal efficacy and neonatal safety data in larger cohorts are necessary. The aim of this cohort study is to describe the clinical outcomes after use of G-CSF in pregnancy, as part of cancer treatment, in patients and their offspring registered by the International Network of Cancer, Infertility and Pregnancy (INCIP).

Materials and Methods

Women with cancer and treated with G-CSF during pregnancy, were identified in the INCIP database. The INCIP study has been approved by the ethical committee of the university hospitals of Leuven in Belgium (S25470) and the Erasmus Medical Center in the Netherlands (NL4354607813). The international multicenter study is registered on ClinicalTrials.gov, number NCT00330447. The registry contains both retro- as prospectively collected obstetric and oncological data of women (and their offspring) with a cancer diagnosis in association with pregnancy.

The INCIP database was reviewed for oncological, obstetrical, neonatal and pediatric data, and missing data were requested from participating hospitals. Pregnancy dating was confirmed in all patients by early ultrasound. To define the efficacy of G-CSF in prevention of chemotherapy-induced neutropenia (dose dense regimen or polychemotherapy regimens with a high risk of neutropenia), results of all available maternal blood samples taken before and during chemotherapy until two weeks after the last administration of G-CSF were

retrospectively extracted from patient files. The incidences of maternal neutropenia, leukopenia, anemia and thrombocytopenia were assessed. Grading of neutropenia, leukopenia, anemia and thrombocytopenia was defined according to the Common Terminology Criteria for Adverse Events (CTCAE version 5.0).[300] Neutropenia was divided in grade 1-2 (mild) [absolute neutrophil count (ANC) 1.5x109/L – lower limit of normal (LLN) or ANC 1.0- 1.5x109/L, respectively] and grade 3-4 neutropenia [ANC of 1.0- 0.5x10^9/L or below 0.5x10^9/L, respectively]. Febrile neutropenia was defined as an ANC below 1.0x10^9/L and fever (=>38 degrees °C). Grade 3-4 leukopenia was defined as a white blood cell count (WBC) below 1.0x10^9/L), thrombocytopenia was divided in grade 1-2 (mild) [platelets count (PC) <150x10^9/L] and grade 3-4 (severe) (PC <50 x10^9/L).[300] Anemia was defined as grade 1-2 (mild) [hemoglobin (Hb) 8-10 g/dl] and 3-4 (severe) anemia (Hb level below 8.0 g/dl). Oncological data that were collected were tumor type, chemotherapy regimen, gestational age (GA) at the start of chemotherapy and number of G-CSF administrations.

The neonatal blood samples were taken within 48 hours after delivery. Neonatal neutropenia was defined as absolute neutrophil count (ANC) <1,0x10^9/L, leukopenia as white blood cell count (WBC) <5,0x10^9/L, thrombocytopenia as PC <15x10^9/L, and anemia as Hb less than 14 g/dL.[52,300,305-308] Customized percentiles for birthweight (p) were calculated, adjusted for GA at delivery, parity, ethnicity, body mass index (BMI) and sex of the infant.[146] Neonates were small for gestational age (SGA) if the birthweight was below the 10th percentile. Neonatal outcomes of two twin pregnancies were described separately.

In addition, available data of children included in the long-term prospective follow-up study of the INCIP project were collected. In this follow-up study, children underwent a general physical examination by a pediatrician (including clinical neurological evaluation), cognitive (neuropsychological) tests by a psychologist (see Table SII-V.1 for details) and cardiac evaluation (electrocardiogram (ECG) and echocardiography) by a cardiologist at different time-points. To assess maternal and neonatal outcomes, descriptive analysis (percentages, median and range) were performed.

Results

Out of 2083 patients registered by INCIP, 42 patients with cancer during pregnancy were treated with chemotherapy and G-CSF (Figure 1). The majority of patients was diagnosed with breast cancer (n=35, 83%), followed by non-Hodgkin lymphoma (n=5, 5%), Ewing sarcoma (n=1, 1%) and acute lymphocytic leukemia (ALL) (n=1, 1%) (Table 1).

Treatment

The median GA at the start of chemotherapy was 22 weeks (range 11-36). One patient started chemotherapy for stage 3 breast cancer at 11 weeks of gestation and delivered of twins without malformations, in all other patients chemotherapy was initiated after 13 weeks of gestation. Both short-acting (filgrastim) and long-acting G-CSF (pegfilgrastim, lipegfilgrastim) were administered for the following indications:

- Long-acting G-CSF was mostly given as part of a dose dense schedule (n=28; 67%).
- Five patients (12%) developed grade 3-4 neutropenia (including one patient with neutropenic fever) after one to three cycles of 3-weekly chemotherapy (without G-CSF). Two of them received filgastrim during the acute episode of neutropenia and all five patients had long-acting G-CSF with the subsequent chemotherapy (without treatment delay) administrations in prevention of febrile neutropenia or dose delays.
- Seven women (7%) received long-acting G-CSF following 'high risk' polychemotherapy for Non Hodgkin lymphoma (n=4), Ewing sarcoma (n=1) or ALL (n=1).
- Long-acting G-CSF (pegfilgastrim) was given prophylactically after the last chemotherapy before delivery in two women (5%).

Figure 1: Study Flow Chart

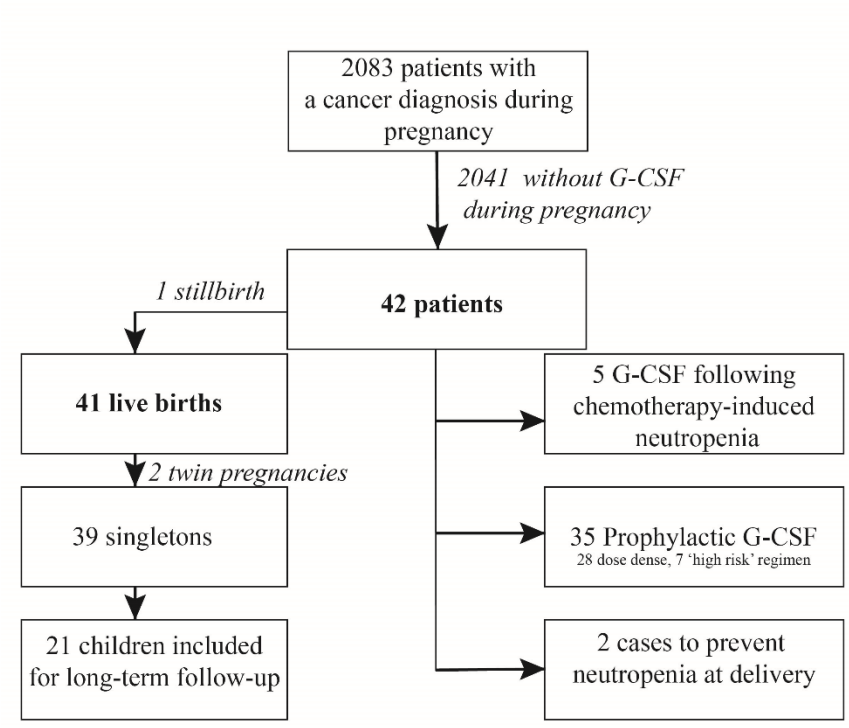

Table 1: Maternal characteristics (n=42)

	Median	Range
Age at diagnosis (years)	34	19 – 47
BMI at booking (kg/m²)*	25.9	18.3 – 36.9
	Number	**%**
Ethnicity		
Caucasian	32	76.2
Non-caucasian	6	14.3
Not reported	4	9.5
Type of malignancy		
Breast cancer	35	83.3
Non Hodgkin lymphoma	5	11.9
Ewing sarcoma	1	2.4
Acute lymphocytic leukemia	1	2.4
Treatment modality		
Chemotherapy	28	66.7
Chemotherapy + surgery	14	33.3
Chemotherapy		
Anthracycline-based	18	42.9
Anthracycline-based with taxanes	15	35.7
Other**	9	21.4
	Median	**Range**
Gestational age at 1st chemo (weeks)	22	11 – 36
Cycles of chemotherapy during pregnancy	6	1-16
Administrations of G-CSF	4	1-16
	Number	**%**
Indication G-CSF		
Prophylactic in dose dense chemotherapy	28	66.7
Propyhlactic in polychemotherapy regimen	7	16.7
Profylactic before delivery	2	4.8
Following chemotherapy-induced neutropenia	5	11.9
Type of G-CSF		
Pegfilgrastim	28	66.7
Lipefilgrastim	8	19.1
Filgrastim	3	7.1
Not reported	3	7.1

*of 5 patients BMI was not available

**Other chemotherapy regimens include R-CHOP (rituximab, doxorubicin, cyclophosphamide, vincristine, prednisone), EP (etoposide, cisplatin),VIDE (vincristine, ifosfamide, doxorubicin, etoposide), R-ACVPB (rituximab, doxorubicin, cyclophosphamide, vindesine, bleomycin, prednisone), EC+TC (epirubicin, cyclophosphamide, paclitaxel, carboplatinum), VIM (ifosfamide, etoposide, without methotrexate during pregnancy), Hyper-CVAD course A (cyclophosphamide, vincristine, doxorubicin, cytarabine, no Methotrexate during pregnancy)

Maternal blood results

Blood results of 24 women who received dose dense chemotherapy were registered (Table 2). Uncomplicated neutropenia grade 3-4 occurred in three women (13%) with breast cancer, but all recovered within five days. There were no reports of febrile neutropenia, nor thrombocytopenia. Mild anemia occurred in 14 women (58%) and severe anemia in two (8%) women. Three patients with available blood counts received long-acting G-CSF as part of intense polychemotherapy with a high risk for neutropenia. One patient suffered from a pancytopenia severe anemia, severe thrombocytopenia and WBC <0.1x109/L) following VIDE chemotherapy (vincristine, ifosfamide, doxorubicin, etoposide). Two patients received R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone) with pegfilgastrim and did not develop hematological toxicities, except for mild anemia in one patient.

Table 2: Maternal blood results following dose dense chemotherapy during pregnancy (n=24 with available serial blood tests following G-CSF)

	Total n *		Grade 1-2		Grade 3-4	
	n	%	n	%	n	%
Neutropenia	5	21	2	8	3*	13
Leukopenia*	4	17	2	8	2	8
Thrombocytopenia	0	0	0	0	0	0
Anemia	16	67	14	58	2	8

*one patient had grade 3 neutropenia ($0.58x10^9$/L) without leukopenia ($3.2x10^9$/L)

Obstetric outcome

The obstetric outcomes of 40 singleton pregnancies are described in Table 3. One patient developed febrile neutropenia and secondary pharyngitis following the first course of FEC (5-fluorouracil, epirubicin, cyclophosphamide) chemotherapy (without G-CSF). Three other patients had a maternal infection requiring antibiotics (two patients with pneumonia, one with a postpartum systemic infection) without leukopenia/neutropenia. An earlier mentioned patient developed a pancytopenia and chorio-amnionitis (without any prior invasive prenatal procedures) and spontaneously delivered a growth-restricted stillborn neonate at a GA of 23 weeks. All other 41pregnancies ended in live births (including two twin pregnancies). Labor was induced in 18 patients (45%), mostly because of maternal therapy planning (78%). Of the 19 pregnancies that ended pre-term (49%), 12 had a planned delivery, of whom 8 (67%) for therapy planning. The seven other women delivered preterm after spontaneous onset of labor. In total, 23 women (55%) delivered within 3 weeks after the last chemotherapy administration, of whom 11 women (25%) delivered within two weeks (7 spontaneous labors, two emerging obstetrical reasons, two planned deliveries for oncological treatment). Emergency caesarean sections were performed in three women because of pre-eclampsia, fetal distress and prolonged second stage of labor, respectively.

Table 3: Obstetric outcomes (n=40, all singleton pregnancies)

	n	%
Live birth	39	97.5
Still Birth	1	2.5
Gestational age at delivery (n=39*)		
≥37 weeks (a term)	20	51.3
< 37 weeks (pre term)	19	48.7
Onset of labor		
Spontaneous	13	32.05
Induction of labor	18	45.0
Cesarean section	9	22.5
Emergency (fetal distress)	2	22.2
Elective (all for obstetrical reason**)	7	77.8
Reason induction of labor (n=18)		
Obstetrical reason***	1	5.6
Therapy planning	14	77.8
Deterioration of maternal condition	2	11.1
Other	1	5.6
Mode of delivery		
Vaginal delivery	27	67.5
Assisted vaginal delivery	2	5.0
Elective Cesarean section	8	20.0
Emergency cesarean section	3	7.5
Complications		
Maternal infection (including 1 chorioamnionitis)	4 (1 postpartum)	10.0
Gestational diabetes	1	2.5
Preeclampsia	1	2.5
Maternal neutropenia/leukopenia	7	17.5
PPROM or preterm contractions	9	22.5
Stillbirth	1	2.5
Postpartum hemorrhage	2	5.0

* 1 stillbirth was excluded

**placenta previa, repeat cesarean section, breech

***hypertension, preeclampsia, cholestasis, diabetes, premature rupture of membranes

Neonatal outcome

Nineteen singleton livebirths were born preterm (19 of 39, 49%). Of all singleton neonates, 11 (28%) were SGA. Thirteen neonates (41%) were admitted to the NICU, mainly because of prematurity (81%) (Table 4). There were no reports of neonates with leukopenia or neutropenia and there were two neonates, born term, with anemia (Hb measurements between 12.0 and 13.5 g/dl). One neonate born one day after prenatal polychemotherapy by emergency cesarean section at a GA of 29 weeks for fetal distress, suffered from a Klebsiella sepsis with thrombocytopenia and intravascular coagulation leading to microthrombi. Two other neonates, delivered preterm within 3.5 weeks following chemotherapy, were treated with antibiotics because of systemic infection. Two neonates had a congenital malformation: one neonate prenatally exposed to FEC (5-FU, epirubicin, cyclophosphamide) (+ pegfilgastrim) and docetaxel from 20 weeks of pregnancy onwards, was born with an absent uvula. The other neonate, prenatally exposed to dose dense AC (doxorubicin, cyclophosphamide) between 30 and 36 weeks of gestation, had a severe pulmonary valve stenosis, diagnosed after birth. It was successfully treated with balloon dilatation at the age of 1 month. In both cases there were no maternal risk factors for congenital malformations, nor neonatal chromosomal abnormalities reported.

Table 4: Neonatal outcomes (n=39, all singleton live births)

	Median	Range
Birth weight (grams)	2855	850-3780
	n	**%**
Customized birthweight percentile		
<10	11	28.2
11-49	18	46.1
50-89	8	20.5
>90	2	5.1
APGAR at 5 minutes		
4	1	2.6
9	8	20.5
10	29	74.4
Not reported	1	2.6
Congenital malformation		
yes	2	5.1
no	37	94.8
Admission neonatal care unit		
yes	16	41.0
no	20	51.3
Not reported	3	7.7
Reason admission neonatal care unit		
Prematurity	13	81.3
Observation because of maternal chemotherapy	1	6.3
Other	2	12.5
Neonatal blood results		
Leukopenia*	0	0
Neutropenia**	0	0
Thrombocytopenia***	1	5.8
Anemia****	2	10
Neonatal complications		
Hyperbilirubinemia	2	5.2
Neonatal sepsis	3	7.7
First degree cerebral bleeding related to prematurity	1	2.6

*Available WBC n=24, **Available ANC n=12, ***Available PC n=18; **** Available hemoglobin n=20

One women delivered of healthy twins following induced labor at 37 weeks after dose dense EC (epirubicin, cyclophosphamide) and paclitaxel weekly. Another twin pregnancy ended in a spontaneous delivery at 29 weeks after dose dense EC and paclitaxel weekly.

Pediatric outcome

Twenty-one children participated in the follow-up study of the INCIP. The median follow-up was 18 months (range 2 months – 9 years) (Table SII-V.1). No neurological or functional cardiac abnormalities were observed. In four children (19%), born at a median GA of 38 weeks, motor development was delayed at 11 months (n=1) and 18 months (n=3). One child had a hip dysplasia and one child had a preferential posture, which both required physiotherapy. Eventually, all four children had a normal motor development at 18 months and 36 months of follow-up according to standardized and clinical measures of development. In four children (19%), delayed cognitive development was identified; one child born at a GA of 29 weeks and 2 days, was assessed at 18 months of age and had an appropriate cognitive development but delayed language development. The child was referred to a speech-language therapist. Two children (10%), both born after GA of 37 weeks, had a delay in cognitive development at 18 months of age, but cognitive development was appropriate at 3 and 6 years of age according to standardized and clinical measures of neurocognitive development. Another child, prenatally exposed to nicotine, cannabis and chemotherapy, was born at a GA of 35 weeks and 4 days with a birthweight of 2060 grams (P 5.1). The child had an appropriate cognitive development at 18 months of follow-up, but cognitive and language development was delayed at 3 years of age. At the age of 3 years, the child also had behavioral and emotional problems and bodyweight was above the 97th percentile. The child and parents were referred to a specialized center for childcare.

Discussion

In this manuscript, we report the maternal and neonatal outcomes of 42 patients with chemotherapy and G-CSF treatment during pregnancy. In the 24 patients that received dose dense chemotherapy supported with G-CSF , febrile neutropenia did not occur and grade 3-4 maternal neutropenia could often be prevented (n=3; 13%). There was one stillbirth following maternal pancytopenia and chorio-amnionitis after VIDE chemotherapy, despite administration of G-CSF to prevent hematological toxicity. Two out of 39 singletons had a congenital malformation (5%). Neonatal neutropenia did not occur and there were no major abnormalities reported in the clinical follow-up of 21 children.

Of note, G-CSF in pregnancy should only be considered when there is a clear indication. There is no evidence to support prophylactic use of the drug prior to delivery, as done in two cases in this series. Outside pregnancy, the addition of G-CSF to chemotherapy improves overall survival, as it minimizes treatment delays and allows dose-dense chemotherapy regimens leading to an increased disease control.[309] The risk of neutropenic fever during chemotherapy in pregnancy is unknown, but may be lower than outside pregnancy owing to the more rapid clearance of chemotherapy and larger distribution volume in pregnancy.[126] However, the consequences of febrile neutropenia in pregnancy threaten both maternal and fetal survival. G-CSF is usually well tolerated, with medullary bone pain being the most frequently reported side effect.[310] Other less common adverse effects include headaches, generalized musculoskeletal pain and, very rare, an anaphylactic-like reaction. An increased risk of secondary hematological malignancies in cancer patients receiving G-CSF is suggested, although this association has not been found consistently and might be also related to increased doses of chemotherapeutic agents with leukemogenic potential.[309,311] Also, patients with severe congenital neutropenia treated with G-CSF, are at long-term risk to develop myelodysplastic syndrome and acute myeloid leukemia.[312] Another concern is that G-CSF might contribute to a hypercoagulable state and thrombosis, besides other factors in this high risk population (pregnancy, cancer, surgery and chemotherapy).[313,314]

Physicians are hesitant to use antenatal G-CSF as it crosses the placenta and could affect the development of the unborn child, including spontaneous miscarriage and congenital malformations.[315] Although there are reassuring data on G-CSF use in neonates, these data cannot just be generalized to the fetus because of the immature fetal metabolism and organs.[316] The neonatal consequences of G-CSF in pregnancy have mainly been investigated for treatment of neutropenia unrelated to chemotherapy. Four large studies and five case reports, with in total 162 pregnancies, have investigated G-CSF in pregnancy for treatment of chronic neutropenia.[315,317-324] In these studies G-CSF administration ranged from the first to the third trimester. None of these studies found an increased incidence of fetal death or congenital malformations. In four pregnancies where G-CSF was used because of ritodrine (a tocolytic drug) induced neutropenia, no maternal or neonatal adverse effects of G-CSF were found.[325,326] Furthermore, it is suggested that G-CSF can be administered in pregnancy or lactation in order to mobilize stem cells for stem cell transplantation.[327] Although, these data are

reassuring concerning G-CSF use, patients were not comparable to our cohort as they did not receive (dose dense) chemotherapy, which is an extra risk factor for adverse maternal and neonatal outcome.

Neonates born from 12 mothers that received G-CSF just before delivery, were shown to have increased neutrophil counts compared to a control group.[299] La Nasa et al reported an incidence of neonatal neutropenia and leukopenia after chemotherapy and long-acting G-CSF of only 4% (n=24 and n=26, respectively).[52] Using the same definitions, we did not observe any neonatal neutropenia or leukopenia in this series. These results suggest that G-CSF may not only be beneficial for the mother but also for the neonate as the prevention of leucopenia will reduce the risk of infection. In this series there were three neonates with an early onset systemic infection without maternal neutropenia. All three neonates were born preterm (between GA of 28-34 weeks) and were SGA, both risk factors for neonatal sepsis.[328]

The incidence of SGA in this population was 28% and 41% of neonates were admitted to the NICU, mostly because of prematurity, which is comparable to large cohort studies on pregnant women with cancer (21% and 41%, respectively).[100] Major congenital malformations are estimated to occur in 255 out of 10,000 births (2.5%).[329] In this series two birth defects (5%) were reported: pulmonary valve stenosis and absent uvula. The latter is an extremely rare condition and based on the registered data it is not clear whether this malformation was isolated or part of a congenital syndrome. Of note, G-CSF and chemotherapy were administered in all patients after the most vulnerable period of fetal organogenesis (between 2 and 8 weeks following conception).[39] As G-CSF has no cytotoxic mechanism of action it is assumable that the causality with congenital malformations is unlikely, but safety in the first trimester cannot be guaranteed based on this series. In comparison, the occurrence of congenital malformation in the pregnant cancer population is reported to be 4% (2% major and 2% minor malformations).[100] In 726 women treated with chemotherapy during pregnancy after 12 weeks of gestation, 22 (3.0%) major and 13 (1.8%) minor congenital malformations were present in the offspring (*INCIP data not published*).

The rate of severe neutropenia following dose dense chemotherapy was 13% (3/24), which is comparable with the reported rates in the non-pregnant population (14.9%).[330] However, the decrease in leukocytes following chemotherapy in pregnancy might be underestimated when reference counts from the general population are used, as during pregnancy the leukocyte count significantly increases physiologically.[331] The observed rate of severe anemia was higher compared to the non-pregnant population (8% vs 2%), however the incidence of mild anemia was comparable (58% vs 66%).[330] Of note, gestational changes induce a 'physiological dilutional' anemia, resulting in reduced physiological Hb levels (10 to 11 g/dl), but severe anemia is unlikely to be explained by pregnancy alone.[332] Of note, there was no report of febrile neutropenia nor thrombocytopenia following dose dense treatment in this series. Major neurologic or functional cardiac abnormalities were not found during follow-up of 21 children. Earlier studies showed that prematurity is a predictor for worse cognitive outcome rather than prenatal exposure to cancer treatment.[40] In addition to this series, no significant

difference in incidence of behavioral problems, asthma, eczema, or problems with speech were found between 29 exposed children, with a mean follow-up of 54 months, and 114 non-exposed children.[304] Of note, available data are still too limited to make robust conclusions and highlights the need for continuous follow-up, especially as children born SGA seems to be at risk for neurological dysfunction.[333]

The maternal and neonatal outcomes in this series are in line with previously published cohort studies of 10 and 34 pregnant women that received G-CSF during oncological treatment.[303,304] A strength of this study was the information on pediatric outcomes after antenatal G-CSF, collected as part of an international registration study. The retrospective nature of the registration study incorporates inevitably missing data. Reported numbers are too low to distinguish consequences of short- and long-acting G-CSF separately. The follow-up of children in this series (maximum 9 years) is also too short to learn about childhood malignancies. Research in larger cohorts remains indispensable to confirm the independent benefit and low incidence of adverse events of G-CSF in the pregnant population and their offspring.

Conclusion

Since we did not observe any marked increase in perinatal complications and the outcomes of this series are in line with available literature, we conclude with caution that the use of G-CSF during pregnancy can be considered when this is clinically indicated for maternal oncological treatment. However, our study was not powered for perinatal complications with low incidence, such as thrombosis, or delayed long-term effects, including secondary malignancies. G-CSF should therefore continue to be administered with caution, and only for indications which provide proven benefit for survival and cancer prognosis, and preferably in the context of ongoing registration studies. These data further contribute to the policy to treat pregnant cancer patients as much as possible as non-pregnant cancer patients in order to prevent worse cancer outcomes.

Part III - IMPACT OF CHEMOTHERAPY DURING PREGNANCY ON FETAL GROWTH

Chapter VI - Impact of chemotherapy during pregnancy on fetal growth

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Abstract

Background

Chemotherapy crosses the placenta, however it remains unclear to what extent it affects fetal growth. The current literature suggests up to 21% of the offspring of women receiving chemotherapy are small for gestational age (SGA, birth weight < 10th percentile). Limiting research to birth weights only might misjudge fetal growth restriction (FGR) in this high-risk population with multiple risk factors for impaired fetal growth. Moreover, the role of the duration of chemotherapy and gestational age at initiation of chemotherapy in fetal growth is yet poorly understood.

Objective

This retrospective cohort study evaluates fetal growth and neonatal birthweights in pregnant women receiving chemotherapy.

Study Design

All pregnant patients, registered by the International Network of Cancer, Infertility and Pregnancy (INCIP), treated with chemotherapy with at least two ultrasounds reporting on fetal growth, were eligible for this study. Duration and gestational age at initiation of chemotherapy were our major determinants, followed by cancer type and stage, maternal characteristics (parity, BMI, ethnicity hypertension, diabetes) and individual cytotoxic agents (anthracycline, taxanes, platinum). Fetal growth outcomes were described using the following mutually exclusive groups 1) FGR, based on a Delphi consensus (2016); 2) 'low risk SGA' (birth weight below the 10th percentile), but an estimated growth above the 10th percentile; 3) 'fetal growth disturbance, which did not meet all FGR criteria; 4) 'non-FGR'. Obstetric and oncological characteristics were compared between the growth impaired groups and non-FGR group.

We calculated estimated fetal weight (EFW) according to Hadlock's formula (1991) and birth weight percentile according to Nicolaides (2018). We used univariable and multivariable regression, and linear mixed effect models to investigate the effect of duration and gestational age at initiation of chemotherapy on birth weight, and fetal growth, respectively.

Results

We included 201 patients, diagnosed with cancer between March, 2000 and March, 2020. Most patients were diagnosed with breast cancer (n=132, 66%). Regimens included anthracyclines (n=121, 60%), (anthracyclines and) taxanes (n=45, 22%) and platinum (n=35, 17%). Fetal growth abnormalities were detected in 75 pregnancies: 43 (21%) FGR, 10 (5%) low risk SGA and 22 (8.5%) fetal growth disturbance. Chemotherapy prior to 20 weeks of gestation (47% vs 25%, p=0.04) and poor maternal gestational weight gain (median percentile 15 (range 0-97) vs 8 (0-84), p=0.03) were more frequent in the FGR group compared to the non-FGR group,

whereas no difference was seen for specific chemotherapy or cancer types. Univariable regression identified gestational weight gain, hypertension, systemic disease and maternal BMI as confounders. Multivariable regression revealed that each additional week of chemotherapy was associated with lower birth weight percentiles (-1.06; 95%CI -2.06; -0.06; p=0.04), and that later initiation of chemotherapy was associated with an increase in birth weight percentile (1.12 per week; 95%CI 0.27; 1.97; p=0.01). Each additional week of chemotherapy was associated with lower EFW and abdominal circumference (AC) percentiles (-1.77; 95%CI -2.21; -1.34, p<0.001; -1.64 95%CI -1.96;-1.32, p<0.001, respectively).

Conclusions

This study demonstrates that FGR is common after chemotherapy in pregnancy, and that the duration of chemotherapy has a negative impact. Sonographic follow-up of fetal growth and well-being is recommended.

Introduction

When cancer is diagnosed during pregnancy, treatment should adhere as much as possible to standard recommendations for non-pregnant patients, including the administration of chemotherapy.[4,5] Chemotherapy has the potential to influence fetal development and growth directly by crossing the placenta.[39] Hence, cytotoxic agents should be avoided during the period of fetal organogenesis.[39] Indirect adverse effects of chemotherapy can be mediated by secondary poor maternal nutrition, hematological toxicity and impaired placental function.[67] The largest cohort study to date on pregnant patients with cancer revealed a high occurrence (21%) of small for gestational age (SGA), defined as a birth weight below the 10th percentile, and antenatal chemotherapy was one of the risk factors.[100] SGA is often used as a proxy for fetal growth restriction (FGR). FGR is defined as a fetus that does not reach the intrinsic growth potential and is diagnosed based on specific ultrasound criteria.[102] Distinction between SGA and FGR is important as FGR represents pathological growth with the highest associated perinatal morbidity and mortality.[102,103] Moreover, the definition of SGA includes constitutionally healthy SGA fetuses with normal outcomes, however misses growth impaired fetuses with a birth weight within normal limits.[104]

The literature on fetal growth abnormalities related to chemotherapy has several limitations. Cancer and pregnancy rarely coincide, occurring in approximately one per 1000 pregnancies, which complicates conduction of prospective studies.[7] As preterm delivery for oncological reasons is common and impaired fetal growth may only occur in the third trimester of pregnancy, the exact incidence of chemotherapy-related FGR might be underestimated. Secondly, SGA does not properly represent FGR, as mentioned above. Thirdly, besides antenatal chemotherapy, multiple other morbidities in the pregnant cancer population, such as high maternal age, stage of disease, nutritional status, co-medications and cancer-related stress might negatively impact fetal growth.[71] Additionally, cancer patients usually receive multiple agents, complicating the interpretation of single agents effects.

The primary aim of this cohort study was to assess fetal growth and the occurrence of FGR in pregnancies exposed to chemotherapy for cancer, who were registered by the International Network of Cancer, Infertility and Pregnancy (INCIP).[2] Additionally, the impact of the duration and the gestational age at initiation of chemotherapy, as well as the impact of specific cytotoxic agents and cancer characteristics, on neonatal birth weight was investigated.

Materials and Methods

Data collection and inclusions

In 2005, INCIP initiated a registry of retro- and prospectively collected oncological and obstetric data of young women with cancer (Clinicaltrials.gov, number NTC00330447). This study was approved by the Ethical Committee of University Hospital Leuven (Belgian number B322201421061) and local approval was obtained

from participating centers when indicated. From the INCIP database, all singleton pregnancies with antenatal chemotherapy and prenatal scan information were selected. Available prenatal scans (range 22-37 weeks of gestational age) were allocated according to the gestational age at execution: '24 weeks' (between 154 and 195 days) and/or '30 weeks' (between 196 and 230 days) and/or '34 weeks' (between 231 and 264 days). Only women with available scans belonging to two different interval groups, with an interval of at least two weeks, were eligible for the study. Cases with major neonatal congenital malformations were excluded. Obstetric and oncological data were collected.

Data processing and definitions

Systemic disease included TNM or FIGO stage IV disease and locally advanced disease with organ dysfunction. Duration of antenatal chemotherapy was defined as the interval between the first exposure and the last exposure during pregnancy, adding the duration of one chemotherapy cycle or the duration from last exposure to birth if the patient delivered earlier. Maternal weight gain was expressed in percentiles, according to the reference range for gestational age at delivery and pre-pregnancy BMI in a low risk pregnant population reported by Santos et al.[147]

The percentiles for measurements of fetal head circumference (HC), abdominal circumference (AC) and femur length (FL) were assessed by the reference range for gestational age of Snijders et al.[334] The EFW from each examination was derived from Hadlock's formula, based on HC, AC and FL.[335] EFW and birth weight by gestational age were expressed as crude percentiles, reported by the Fetal Medicine Foundation.[336] We used this international reference chart as it was designed to overcome the problem of underestimation of FGR in preterm birth, by providing information at all gestational ages, including babies in utero. If neonates had a birth weight below the 10th customized percentile, they were defined as SGA. Customized percentiles were calculated for birth weight, corrected for gestational age, ethnicity, neonatal gender, maternal pre-pregnancy BMI and parity.[146] Placental weight was corrected for gestational age at delivery.[337] Abnormal Doppler measurements were defined as Pulsality index (PI) of the umbilical artery >95th percentile according to the references by the Fetal Medicine Foundation.[338]. The cerebroplacental ratio is defined as the ratio of the middle cerebral artery PI to the umbilical artery PI and assumed abnormal when <5th percentile.[338]

Based on ultrasonographic features and birth weight, pregnancies were allocated into four mutually exclusive groups according to fetal growth impact;

1) FGR based on birth weight percentile below the 3rd percentile or ultrasonographic features defined by a Delphi consensus in 2016 (*the FGR group*).[102,339] FGR before 32 weeks (early FGR) was defined as an AC or EFW percentile below the 3rd percentile or absence of end-diastolic umbilical flow or AC/EFW below the 10th centile in combination with abnormal Dopplers of the uterine artery or the umbilical artery (above the 95th percentile). FGR after 32 weeks (late FGR) was defined as AC/EFW below the 3rd percentile or at least two out of three of

the following; EFW below the 10th percentile, AC/EFW crossing ≥50 growth percentiles and/or cerebroplacental ratio below 5th percentile and/or Doppler of umbilical artery above the 95th percentile. Asymmetrical FGR was defined by an HC/AC ratio greater than the 95th percentile.[334]

Because of the inherent poor predictive value of ultrasound, a second and a third group 'at risk' were defined.

2) A second group included cases with a birth weight percentile below the 10th percentile, that otherwise did not meet any of the criteria for FGR (*the 'low risk SGA' group*).

3) A third category 'at risk' for fetal growth impact was defined when only one of the following features was present at the prenatal ultrasound: a decrease in AC/EFW of ≥50 centiles during the course of pregnancy or EFW/AC percentile below the 10th percentile (*the 'fetal growth disturbance' group*).

4) The fourth category included all cases without growth abnormalities (*the 'normal fetal growth' group*)

Statistical Analyses

Descriptive statistics are presented as frequencies with percentages for categorical variables, or median with range and interquartile range for continuous variables. Oncological features and obstetric outcomes were compared between pregnancies with growth impact (FGR, 'low risk SGA group', 'fetal growth disturbance') and pregnancies without (non-FGR), using Chi square for categorical variables or Fisher exact test in case of frequencies lower than five, and Mann Whitney U test for continuous variables. Multivariable linear regression models were used to evaluate the effect of duration of antenatal chemotherapy and gestational age at initiation on fetal growth and crude birth weight percentile. Confounders were included in the models if they showed a significant association with fetal growth in the univariable analysis ($p<0.2$) or if identified as clinically relevant. In addition, ethnicity, parity and neonatal gender were added to the multivariable models. A linear mixed-effects model (LME) for repeated measures was used to identify the possible influence of initiation and total duration of chemotherapy on fetal growth, assessed by biometric measurements (EFW, AC, HC and FL).[340] All tests were two-sided, and a p=5% threshold for statistical significance was assumed for all tests. Analyses were performed using SAS software (version 9.4 of the SAS System for Windows) and R (version 3.6.0).

Results

Study population

Out of 1008 pregnancies with antenatal chemotherapy registered in the INCIP database, 201 women were eligible (Figure SIII-VI.1). Between all INCIP cases, including those with <2 prenatal scans, and our study group no significant difference was observed with regard to birth weight percentile (Table SIII-VI.3). Most women were diagnosed with breast cancer (132, 66%) and anthracyclines were the most frequently administered chemotherapeutic agent (158, 79%) (Tables 1a and 1b). Overall, sonographic percentiles of EFW, HC, AC and FL showed a decreasing trend, when comparing 24, 30 and 34-weeks scan results in 107 cases with ultrasounds at all of these timepoints (Figure SIII-VI.2). However, boxplots of these measurements revealed a stable, wide range from percentile 0 to 100 percentiles. Of note, 76 of 107 women (71%) had already initiated chemotherapy by the 24-weeks scan. The median birth weight percentile for the INCIP population was 30 (range 1-100) (Figure 1).

Figure 1: Scatter plot of birthweight according to gestational age at delivery, plotted on the reference chart by Nicolaides et al., 2018[337] (n=201)

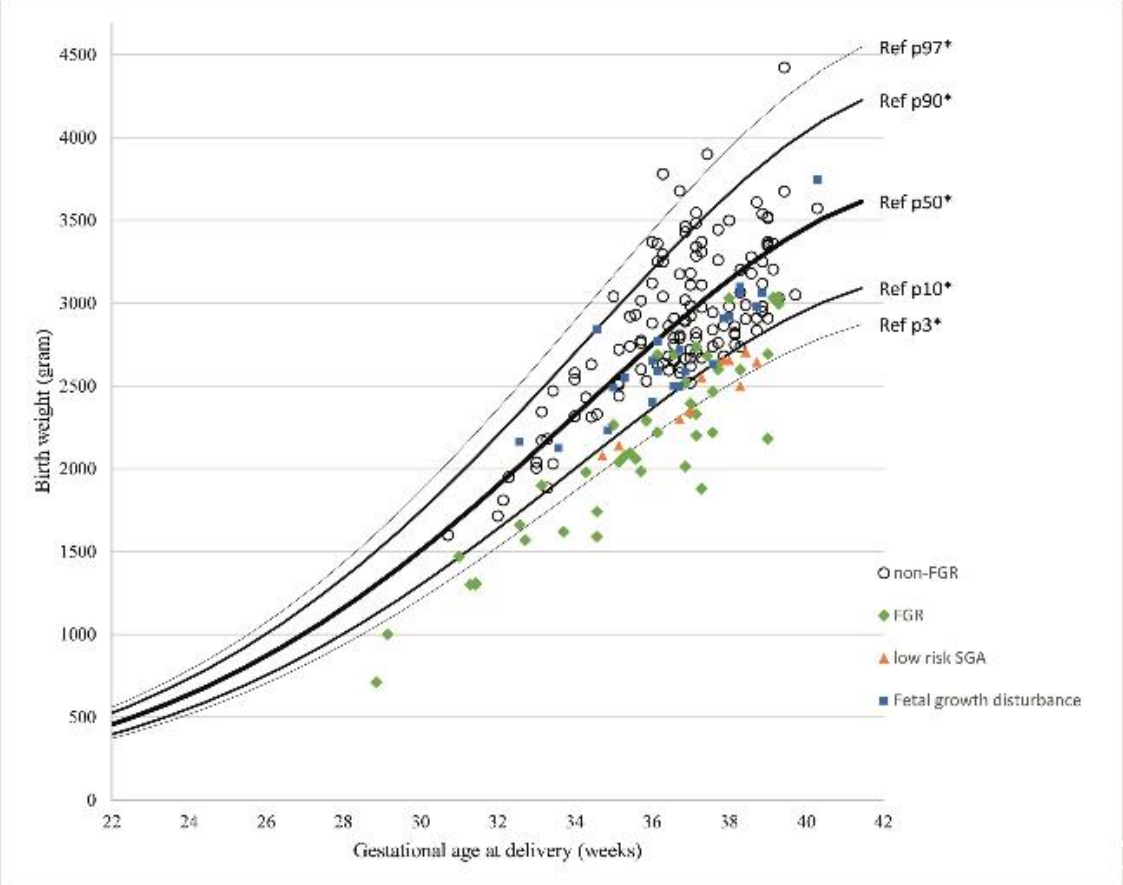

Table 1a: Characteristics (continuous variables) by groups. The characteristics of the Fetal Growth Restricted (FGR) group, 'low risk SGA' group and 'fetal growth disturbance' group are compared to the group with normal fetal growth (Non-FGR).

	Total	Non-FGR	FGR	p-value	Low risk SGA	p-value	Fetal growth disturbance	p-value
Total N *For maternal BMI at booking* *For maternal weight gain* *For placenta weight and percentile*	**201** *170* *151* *176*	**126** *106* *83* *91*	**43** *38* *33* *27*		**10** *8* *8* *7*		**22** *18* *17* *16*	
Maternal age at diagnosis (years)	33 (33-19; 46)	34 (21-45; 6)	33 (24-46; 8)	0.598	33 (24-43; 10)	0.254	33 (19-41; 7)	0.280
Maternal BMI at booking (kg/m2)	24 (16-42; 7)	25 (18-42; 7)	22 (16-38; 5.9)	0.021	24 (19-28; 4)	0.263	25 (19-33; 3)	0.927
Gestational weight gain (kg)	7 (-9–25; 6)	7 (-7-25; 7)	5.9 (-9–18; 5)	0.085	8 (2-22; 4)	0.820	7 (1–16; 6)	0.473
Maternal weight gain (percentile) (Santos)*	13 (0-97; 32)	15 (0-97; 37)	8 (0-84; 28)	0.033	7 (0-96; 21)	0.197	10 (1-74; 27)	0.473
GA chemo initiation (weeks)	22 (12-34; 9)	23 (12-34; 8)	20 (13-32; 10)	0.042	17 (16-22; 5)	0.004	22 (12-33; 10)	0.325
Duration of chemo during pregnancy (weeks)	12.3 (2-26; 7)	2 (2-26; 7)	12 (3-22; 8)	0.560	16 (7-20; 5)	0.026	14 (3-24; 9)	0.284
Number of courses of chemotherapy	5 (1-16; 3)	4 (1-16; 3)	4 (1-16; 4)	0.715	7 (5-12; 7)	0.002	6 (1-16; 6)	0.134
GA delivery (weeks)	37 (29-40; 3)	37 (31-40; 2)	36 (29-39; 3)	0.046	38 (35-39; 2)	0.393	37 (33-40; 3)	0.499
Crude birthweight percentile	30 (1-100; 46)	47 (10-100; 52)	3 (1-39; 14)	<0.001	7 (3-9; 5)	<0.001	28 (10-90; 23)	0.002
Customized birth weight percentile**	32 (0-99; 47)	46 (4-100; 44)	4 (0-41; 16)	<0.001	8 (3-17; 9)	<0.001	25 (11-91; 32)	0.032
Placental weight (grams)***	394 (136-750; 158)	435 (243-750; 166)	308 (136-574; 113)	<0.001	294 (199-421; 157)	0.008	391 (332-750; 103)	0.546
Placenta percentile (Thompson)	4 (2-85;13)	8 (2-80; 27)	2 (2-31; 3.3)	0.004	2 (2-3; 0)	0.214	5 (2-85; 11.3)	0.498

For all characteristics the median (range; interquartile range) are given

Abbreviations: BMI: Body Mass Index; cm: centimeter; kg: kilogram; GA: gestational age

*according to the reference range for gestational age at delivery and pre-pregnancy BMI in a low risk pregnant population as reported by Santos et al.

** according to the reference chart reported by Gardosi et al.[146]

*** The INCIP database does not distinct between placental weight based on untrimmed or trimmed measurements, nor fixed or fresh.

Table 1b: Characteristics (categorical variables) by groups. The characteristics of the Fetal Growth Restricted (FGR) group, 'low risk SGA' group and 'Fetal growth disturbance group are compared to the group with normal fetal growth (No impact growth)

	Total		Non-FGR		FGR		p-value	Low risk SGA		p-value	Fetal growth disturbance		p-value
Total N	201		126		43			10			22		
	N.	**%**	**N.**	**%**	**N.**	**%**		**N.**	**%**		**N.**	**%**	
Cancer type							0.847			0.287			0.265
Breast cancer	132	66	81	64	29	67		7	70		15	68	
Gynecological Cancer	23	11	18	14	5	12		0	0		0	0	
Hematological Cancer	39	19	3	2	2	5		1	10		1	5	
Other	7	3	24	19	7	16		2	20		6	27	
US available							0.503			0.894			0.027
all echo (24-30-34)	107	53	60	48	5	58		5	50		18	82	
echo 24-30	53	26	35	28	11	26		3	30		3	14	
echo 30-34	33	16	21	17	6	14		2	20		1	5	
echo 24 and 34	11	5	10	8	1	2		0	0		0	0	
Ethnicity							0.623			1.000			0.746
Caucasian	175	87	108	85	39	91		9	90		19	86	
African	4	2	4	3	0	0		0	0		0	0	
Asian	20	10	12	10	4	9		1	10		3	14	
Other (including hispanic)	2	1	2	2	0	0		0	0		0	0	
GA initiation chemo							0.036			0.011			0.320
<20	68	34	32	25	20	47		7	70		9	41	
20-27,9	92	46	65	51	16	37		3	30		8	36	
≥28 weeks	41	20	29	23	7	16		0	0		5	23	
GA initiation chemo							0.222			0.005			0.198
<16	25	12	12	10	8	19		0	0		5	23	
16-19.9	43	21	20	16	12	28		7	70		4	18	
20-23.924-27,	55	27	38	30	10	23		3	30		4	18	
28-31.9	37	18	27	21	6	14		0	0		4	18	
>32	30	15	23	18	5	11		0	0		2	9	
	11	5	6	5	2	5		0	0		3	14	
Maternal BMI							0.030			0.321			0.686
<18,5	4	2	1	1	3	7		0	0		0	0	
18,5-24,9	91	45	52	41	24	56		6	60		9	41	
25,0-29,9	47	23	32	25	6	14		2	20		7	31	
>30,0	28	14	21	17	5	12		0	0		2	9	
Not reported	31	15	20	16	5	12		2	20		4	18	
Parity							0.278			0.091			1.000
Nulliparous	85	42	49	39	21	49		7	70		8	36	
Multiparous	115	57	77	61	21	49		3	30		14	64	
Not reported	1	1	0	0	1	2		0	0		0	0	
Smoking or substance							1.000			0.623			1.000
No	117	58	76	60	22	51		5	50		4	18	
Yes	30	15	18	14	6	14		2	20		14	64	
Unknown	54	27	32	25	15	35		3	30		4	18	
Hypertensive disorder							0.160			1.000			1.000
No	198	99	125	99	73	95		10	100		22	100	
Yes	3	1	1	2	2	5		0	0		0	0	
Disease extent							0.094			0.604			0.241
Local	178	89	115	91	35	81		10	100		18	82	
Systemic	23	11	11	9	8	19		0	0		4	18	
Diabetes							0.204			1.000			0.592
No	195	97	120	95	43	100		10	100		22	100	
Yes	6	3	6	5	0	0		0	0		0	0	
Treatment							0.103			0.239			0.563
Anthracyclines	121	60	80	65	21	49		5	50		15	68	
(Anthracyclines +)	45	22	22	17	14	32		4	40		5	23	
Taxanes*	35	17	24	19	8	19		1	10		2	9	
Platinum-based													
Anthracyclines							0.525			0.227			0.252
No	43	21	26	21	11	26		4	40		2	9	
Yes	158	79	100	79	32	74		6	60		22	91	
Taxanes							0.812			1.000			0.148
No	141	70	105	83	37	86		9	90		17	77	
Yes	60	30	21	17	6	14		1	10		5	23	
Platina							0.713			1.000			0.766

No	163	81	103	82	59	79		8	80		19	86	
Yes	38	19	23	18	16	21		2	20		3	14	
NICU admission							0.764			1.000			0.695
No	129	64	115	91	38	88		9	90		21	95	
Yes	53	26	11	9	5	12		1	10		1	5	
GA delivery							0.003			0.510			0.554
<32 weeks	7	3	1	1	6	14		0	0		0	0	
32-34 weeks	17	8	11	9	4	9		0	0		2	9	
34-37 weeks	81	40	51	40	15	35		3	30		12	55	
>37 weeks	93	48	63	50	18	42		7	70		8	36	
Onset of labor							0.194			0.123			0.118
spontaneous	45	22	22	17	11	26		4	40		8	36	
IOL	79	39	50	40	19	44		3	30		7	32	
Elective CS	70	35	51	40	11	26		2	20		6	27	
Missing	7	3	3	2	2	5		1	10		1	5	
Spontaneous preterm labor	182	91	117	93	39	91	0.813	9	90	1.000	17	77	0.037
No	19	9	9	7	4	9		1	10		5	23	
Yes													
Reason of IOL (n=79)			N=50		N=19		0.229	N=3		1.000	N=7		0.936
maternal obstetrical	4	5	2	4	2	11		0	0		0	0	
fetal obstetrical	4	5	3	6	2	11		0	0		0	0	
therapy planning	63	80	42	84	11	58		3	100		6	86	
maternal deterioration	7	9	3	6	3	16		0	0		1	14	
other	1	1	0	0	1	5		0	0		0	0	
Reason Elective CS (n=70)			N=51		N=11		0.226	N=2		0.568	N=6		0.599
Maternal Obstetrical	23	33	18	35	2	18		0	0		3	50	
Fetal obstetrical	6	9	4	8	2	18		0	0		0	0	
Maternal clinical/oncological	41	59	29	57	7	64		2	100		3	50	
Mode delivery							0.101			0.176			0.481
Vaginal	112	56	64	51	28	65		7	70		13	59	
Cesarean section	82	41	59	47	13	30		2	20		8	36	
Not reported	7	3	3	2	2	5		1	10		1	5	
Abnormal dopplers							0.001			na			na
No	133	96	85	100	29	85		5	100		14	100	
Yes	5	4	0	0	5	15		0	0		0	0	
Not reported	63		41		9			5			8		
Oligohydramnion							0.037			1.000			1.000
No	195	97	124	98	39	91		10	100		22	100	
Yes	6**	3	2	2	4	9		0	0		0	0	

Abbreviations: GA: gestational age; na: not applicable

* Including four women with breast cancer that only received taxanes during pregnancy

*Treatment with 1. Cisplatin (6x), 2. Doxorubicin-Cyclophosphamide (4x) and paclitaxel (4x), 3. Epirubicin-cyclophosphamide (4x), 4. Doxorubicin-cyclophosphamide (2x), 5. BEACOPP (6x), 6. EPOCH (4x)

Out of 201 cases, 43 patients (21%) delivered a SGA neonate. In total, 75 of 201 (37%) pregnancies were subject to impaired fetal growth according to the predefined definitions; 1) *FGR* occurred in 43 fetuses (21%). Early FGR (<32 weeks of gestation) occurred in 19/43 growth restricted fetuses (44%) and 7/43 growth restricted fetuses (16%) were classified as asymmetrical FGR. In addition, 2) 10/201 neonates (5%) were *low risk SGA* at birth and 3) 22/201 fetuses (17%) were *presumably FGR*. There was one stillbirth at 31 weeks of a fetus that was early (symmetrical) FGR based on sonographic findings. Placental pathology revealed villous fibrosis and a large hematoma.

There were no significant differences in oncological characteristics between *FGR* and *non-FGR* cases. In the FGR group, the maternal weight gain was lower (p=0.033) compared and more women started chemotherapy prior to 20 weeks of gestation (p=0.036). In 144 pregnancies, Doppler studies were reported. All cases with abnormal Doppler measurements were allocated to the FGR group (n=5).

Median gestational age at delivery was 37 weeks (range 29-40). Most deliveries were planned for obstetric or medical reasons (149 of 201, 74%). Only 10/201 (4.9%) women had an planned delivery because of fetal reasons (eg. FGR). Preterm delivery was reported in 105 (65%) women, including 19 women with spontaneous preterm labor (9%).

Effects of chemotherapy on birth weight

Univariable regression analysis showed that early gestational age at initiation of chemotherapy and longer duration thereof, systemic disease, low gestational weight gain, hypertensive disorders and low maternal BMI were associated with lower birth weight percentile (Table SIII-VI.1).

As most women in this series (n=158, 79%) received anthracyclines, and previous research revealed a higher risk for SGA with taxanes and platinum, we corrected for the receipt of taxanes and/or platinum in multivariable analysis.[100] In addition, diabetes, maternal age at diagnosis, and cancer type were identified as important clinically relevant confounders for fetal growth. As the effect of gestational age at initiation of chemotherapy and duration of chemotherapy exposure were highly correlated, both variables could not be used in one model. In multivariable analysis, the duration of antenatal chemotherapy (in weeks) was negatively associated with birth weight percentile (-1.06; 95%CI -2.06; -0.06; p=0.04), and gestational age at initiation of chemotherapy (in weeks) showed a positive correlation (1.12; 95%CI 0.27; 1.97; p=0.01) (Table SIII-VI.1).

Effect of chemotherapy on fetal growth

The linear mixed effects models revealed that a longer duration of chemotherapy (in weeks) was related to lower EFW, AC, HC and FL percentiles (-0.253 95%CI -0.315; -0.191, p<0.001; -0.234 95%CI -0.280;-0.189, p<0.001; -0.200 95%CI -0.034-0.117, p<0.001; and 0.035 95%CI -0.039;0.108, p<0.001 respectively) (Table SIII-VI.2 and Figure SIII-VI.3). In these models, the duration of antenatal chemotherapy appeared to have a greater influence on fetal growth compared to gestational age at chemotherapy initiation. The later chemotherapy was initiated, the higher the negative impact on EFW, AC and HC (with a constant chemotherapy duration).

Discussion

In this cohort study of pregnant cancer patients treated with chemotherapy, of whom 66% had breast cancer, 79% received anthracyclines and 88% delivered after 34 weeks of gestation, we found that over one third of the pregnancies was complicated by impaired fetal growth, including 21% FGR. Disease-related factors that were associated with FGR were systemic disease and low gestational weight gain, both associated with general maternal health and nutrition. The current data show that there is a strong correlation between low birth weight and a longer duration of chemotherapy exposure on the one hand and, likewise, low birth weight and an earlier gestational age at initiation of chemotherapy on the other. Nevertheless, when controlling for chemotherapy duration, it appeared that chemotherapy initiation later in pregnancy resulted in a stronger impairment of fetal growth.

The literature about chemotherapy related FGR describes conflicting results; the largest cohorts, revealed an increased risk of SGA, whereas others, including population-based studies, do not confirm this.[9,12,80,100,341,342] To date, research in this field focused on birth weight only, potentially misjudging or underestimating the problem of FGR. Here, we confirm the high incidence of FGR in pregnant women receiving chemotherapy. However, not all fetuses are growth impaired and the majority do show a reassuring growth. The multifactorial etiology of FGR apart from exposure to cytotoxic drugs, including maternal nutritional status and disease severity, psychological stress, the presence of hypertensive disorders or diabetes, is reflected in these data. Factors interfering with fetal growth will have most impact when occurring in the third trimester of pregnancy, as EFW growth velocity increases across gestation, with a peak acceleration in the third trimester of pregnancy (35 weeks of gestational age).[343]

Both maternal, placental and fetal factors play a role in the etiology underlying FGR.[71] In pregnant cancer patients poor nutrition and general health, primary by cancer and secondary by the adverse effects of cancer treatment and cancer-related stress, are major determinants. In this series, only 21% (32 of 151 data available) patients met IOM standards for maternal weight gain.[344] There is increasing evidence that prenatal stress disrupts maternal and fetal endocrine (cortisol-related pathways involving the hypothalamic-pituitary-adrenal (HPA) axis), nervous and immune (increased cytokine release) systems, hereby affecting pregnancy outcomes, including preterm birth and FGR.[345] Prenatal stress is reported to directly interfere with the insulin growth factor (IGF) system, involved in the regulation of fetal, placental and neonatal growth.[346]

Placental changes following chemotherapy exposure include histologic disturbances related to impaired maternal-fetal nutrient supply as well as placental oxidative damage and apoptosis affecting placental growth and function.[347-349] A case control study, evaluating chemotherapy-exposed placentas from women with cancer and placentas from healthy controls, confirmed increased oxidative (DNA) damage in chemotherapy-exposed placentas, with an increasing effect with longer chemotherapy exposure.[349] Also, chemotherapy

might induce DNA damage and epigenetic changes in the unborn child, affecting growth and health on the long-term.[350]

Follow-up studies of children prenatally exposed to chemotherapy reveal that SGA children will eventually catch up growth.[40,113] This implicates that adverse fetal effects are rather transient, without affecting the postnatal growth potential. It remains unclear whether chemotherapy itself or the disease-related stress and inflammation is the dominant factor in impaired fetal growth; most likely it is a combination thereof.

With the relative low molecular weight and lower plasma protein binding, platinum-derivates will cross the placenta more easily compared to anthracyclines.[48,49,51] Although measured fetal plasma concentrations are low, the strong tissue-binding capacity of taxanes results in measurable concentrations in fetal tissues.[49,351,352] Based on earlier reports we hypothesized that low birth weight percentiles would mainly be seen in patients exposed to taxanes and platinum, but we could not confirm this.[100] However, this cohort is relatively small compared to previous series and the heterogeneous cancer treatments and multidrug use complicate the detection of specific drug interactions.

This cohort study reveals a negative impact of the duration of chemotherapy on fetal growth, however the actual cause of impaired fetal growth is most likely explained by the (longer duration of) exposure to multiple factors including cytotoxic agents, co-medications, maternal physical and psychological stress and malnutrition. In clinical practice, oncological management should adhere to standard protocols, while continuously balancing maternal and fetal risks. In order to preserve maternal prognosis antenatal treatment should not be postponed. Fetal surveillance includes serial growth scans and patients with an oncological diagnosis early in pregnancy and a presumed long antenatal treatment are at highest risk of impaired fetal growth.

This is an observational study to assess FGR in a selected group of pregnant women receiving chemotherapy, based on predefined criteria. However, management of FGR in cancer patients is case-specific and should not be extrapolated from this retrospective series. The variance in numbers of available ultrasound and performed Doppler measurements between patients is a consequence of the difference in local policies in obstetric follow-up of pregnant patients receiving chemotherapy and the lack of an international consensus. The lack of a detailed ultrasound reporting system in some hospitals, explains why relatively few cases with available ultrasounds could be selected from the large INCIP registry. Also, this cohort is subject to selection bias as fetal ultrasounds may have been performed because of an assumed high risk of fetal growth abnormalities. The majority of the participating hospitals counsel pregnant cancer patients in a routine way for INCIP registration. In terms of distribution of cancer types, duration of antenatal chemotherapy and mean birth weight this series appears representative for the INCIP database. The results of this series should be interpreted with caution because multiple confounders for fetal growth in this high-risk population complicate data interpretation.

Because of the retrospective study design, large amount of data were missing (e.g. on BMI, gestational weight gain, smoking/substance use during pregnancy). Also, we could not further explore placental histopathological findings. Future research on antenatal chemotherapy should not only focus on clinical data, but also on placental histopathology and FGR-related biomarkers in order to unravel the exact mechanism of chemotherapy-induced FGR. Larger prospective, more homogeneous cohorts are needed to further focus on effects of specific chemotherapy regimens and investigate a dose-effect of chemotherapy on fetal growth and birth weight, as suggested by these data. Collection of data is challenging and should be organized in a multicenter setting.

Conclusion

This study reveals that prenatal exposure to chemotherapy is a risk factor for FGR. Pregnant cancer patients should be followed in a high-risk obstetric unit with a close surveillance of the fetal growth, especially in the third trimester of pregnancy.

Part IV - MATERNAL ONCOLOGICAL PROGNOSIS

Chapter VII - Outcome of breast cancer patients treated with chemotherapy during pregnancy compared with non-pregnant controls

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Abstract

Background

A diagnosis of breast cancer during pregnancy (PrBC) does not impact prognosis if standard treatment is offered. However, caution is warranted as gestational changes in pharmacokinetics may lead to reduced chemotherapy concentration.

Methods

Survival of PrBC patients treated with chemotherapy during pregnancy was compared to non-pregnant breast cancer patients treated with chemotherapy, diagnosed after 2000, excluding patients older than 45 years or with a postpartum diagnosis. The data was registered in two multicenter registries (the International Network of Cancer, Infertility and Pregnancy and the German Breast Group). Cox proportional hazards regression was used to compare disease-free (DFS) and overall survival (OS) between both groups, adjusting for age, stage, grade, hormone receptor status, human epidermal growth factor 2 status and histology, weighted by propensity scoring to account for the differences in baseline characteristics between pregnant patients and controls.

Results

In total, 662 pregnant and 2081 non-pregnant patients were selected. Pregnant patients were more likely to have stage II breast cancer (60.1% vs 56.1%, p=0.035), grade 3 tumors (74.0% vs 62.2%, p<0.001), hormone receptor-negative tumors (48.4% vs 34.0%, p<0.001) or triple-negative breast cancer (38.9% vs 26.9%, p<0.001). Median follow-up was 66 months. In multivariable analysis, DFS and OS were comparable for pregnant and non-pregnant patients (DFS: HR 1.02, 95%CI 0.82-1.27, p=0.83; OS: HR 1.08, 95% CI 0.81-1.45, p=0.59).

Conclusion

Outcome of women with breast cancer treated with chemotherapy during pregnancy is comparable to young non-pregnant women. These results support chemotherapy for PrBC when indicated.

Introduction

When studying maternal breast cancer prognosis, breast cancer diagnosed during pregnancy (PrBC) should be distinct from breast cancer diagnosed after delivery (PPBC), which has a more aggressive character with worse prognosis.[130] To date, there is no evidence that PrBC impacts oncological prognosis as long as patients are managed by cancer stage according to standards for non-pregnant patients.[4,8] PrBC has the same characteristics as non-pregnancy related breast cancer in young patients and are thus mainly high grade, triple negative in about one third and human epidermal growth factor receptor 2 (HER2) positive in one third..[138] A diagnosis of PrBC often requires consideration of antenatal chemotherapy in order to timely treat and preserve prognosis. Anthracyclines, cyclophosphamide and taxanes can be initiated relatively safe from the second trimester of pregnancy onwards.[4] It is however insufficiently known to what extent gestational physiologic changes, that result in chemodilution, reduce the efficacy of chemotherapy. Indeed, pregnancy is characterized by an increase in plasma volume of up to 34-70%, which is distributed among the fetus, amniotic fluid, and maternal extra- and intracellular spaces.[127] This increased distribution volume reduces the peak plasma drug concentration.[126] In addition, glomerular infiltration rate (GFR) is increased and hepatic metabolism is altered, including upregulation of enzymes in the cytochrome P450 system, which plays a role in the metabolism of chemotherapeutic agents. Hence, these physiologic gestational changes alter the area under the time-concentration curve, with a potential impact on drug efficacy.[126,127] Recent human data reveal a decrease in chemotherapy exposure in pregnant women, variating from 6.3% (epirubicin) to 24.0% (paclitaxel) of the peak plasma concentration in non-pregnant patients.[353]

Because of the fact that clinical trials on PrBC are ethically impossible, most evidence on maternal prognosis comes from multicenter cohort and case control studies, some of them limited by small numbers or lack of detailed information on antenatal treatment.[54,132,133,135,138] The German Breast Group (GBG) and the International Network of Cancer, Infertility and Pregnancy (INCIP) previously joined forces to evaluate obstetric and oncologic outcomes of patients diagnosed with PrBC.[54,138] In the previous comparison of 447 PrBC patients with 865 non-pregnant controls, there was no difference in outcome, although the subgroup of patients that received antenatal chemotherapy was too small to draw firm conclusions.[138] The purpose of this larger cohort study is to add evidence, specifically for the group of patients who received chemotherapy antenatally.

Material and methods

Study design

Two multicenter registries with a focus on cancer during pregnancy collaborated in this study; the GBG initiated registration of PrBC in 2003 whereas INCIP was an European initiative founded in 2014. All registered pregnant patients, diagnosed with stage I-III PrBC between January 1, 2000 and October 31, 2018 who were treated with standard chemotherapy regimens, were included.

For the non-pregnant control group, all stage I-III breast cancer patients younger than 45 years and diagnosed between January 1, 2000 and August 31, 2018 were recruited from the institutional database of the Multidisciplinary Breast Centre (MBC) of the University Hospitals of Leuven and from the non-pregnant cohort of the multicenter GBG registry. From the GBG registry, all patients are younger than 40 years as this is the age limit for recruitment by GBG. Patients with a breast cancer diagnosis within two years after a delivery were excluded for analysis because of the reported inferior survival for postpartum breast cancer cases.[130,354]

All patients included were staged and treated according to local hospital policies. Standard chemotherapy regimens included anthracycline-based therapies AC (doxorubicin, cyclophosphamide) and EC (epirubicin, cyclophosphamide), FAC (5-fluorouracil, doxorubicin, cyclophosphamide), FEC (5-fluorouracil, epirubicin, cyclophosphamide) and anthracycline-taxane-based therapies (docetaxel or paclitaxel) +/- carboplatinum. Regimens were administered at standard of care dosages. Non-standard of care regimens included CMF (cyclosphosphamide, methotrexate, fluorouracil), anthracycline monotherapy and vinorelbine.

Primary outcome was the difference in disease-free survival (DFS) between patients treated with chemotherapy during pregnancy for PrBC and patients not diagnosed during a pregnancy. DFS was defined as time (months) from the date of the first diagnosis until any loco-regional (ipsilateral breast, local/regional lymph nodes) recurrence of disease, any invasive contralateral breast cancer, any distant recurrence of disease, any secondary malignancy or death due to any cause, whichever occurred first. Patients without events were censored at the date of last contact or at the cut-off date. Secondary outcome was the difference in overall survival (OS) between both groups. OS was defined as the time (months) from the date of first diagnosis to the date of death resulting from any cause. Patients alive were censored at the date of the last contact or at the cut-off date.

The observational multicenter registries were approved by ethics committees [University Hospital Leuven (INCIP) and Goethe Universität Frankfurt,Germany (GBG)] and the studies were registered with ClinicalTrials.gov (INCIP study, NCT00330447; GBG study, NCT00196833).

Statistical analysis

Prior to the analyses, a power calculation was performed. Based on the previously published cohort and the hypothesis that antenatal chemotherapy is less effective due to gestational physiological changes, a 5 year DFS was assumed to be 71% for control patients and 61% for pregnant patients (HR=1.443). With 1:1 ratio between pregnant patients and controls, 233 events would be sufficient to have 80% power to the significance level of α=0.05. Adjusting for the 1:3 ratio between pregnant patients and controls and some difference in median follow up between groups, 365 events were considered sufficient. Since censoring after approximately 14 years seemed to be not completely at random (deaths over-reported compared with last contact with patient

alive), an arbitrary cut-off date was defined as the time of the last DFS event in the pregnant group (173 months) + 1 day for survival analyses. Patients with a longer available follow-up were censored.

DFS and OS were compared between pregnant and non-pregnant patients using multivariable Cox proportional hazards regression to adjust for age at diagnosis, stage (I, II or III), grading (gr 1-2 versus gr 3), histologic tumor type (lobular versus non-lobular), estrogen receptor (ER)/progesterone receptor (PR) status (positive or negative), human epidermal growth factor receptor 2 (HER2) status (HER2-negative vs HER2-positive without or unknown anti-HER2 treatment vs HER2-positive with anti-HER2 treatment) and type of chemotherapy (anthracycline-based only, anthracyclines and taxanes, non-standard treatment). Pregnant patients were allocated to the group treated with anthracyclines and taxanes when at least 15% of the scheduled total dose of taxanes was given during pregnancy. Hazard ratio (HR) with 95% confidence interval (CI) were reported as well as a Wald *p*-value for each variable in the analysis. Additionally, Kaplan-Meier curves for DFS and OS were created which should be considered purely descriptive. Given that some baseline characteristics were differently distributed between pregnant women and controls, simply adjusting for those as covariates was not considered sufficient. Instead, an inverse probability weighting by a propensity score based on age, stage, grade, histological tumor type, HR, chemotherapy regimen, HER2 was used for all multivariable analyses.[355] Out of clinical interest, further subgroup analyses for hormone receptor status, stage, age, chemotherapy type and setting (neo-adjuvant versus adjuvant) were performed, and additionally per registry (GBG versus INCIP). In the pregnant group, an exploratory analysis on the number of administrations and the proportion of chemotherapy given during pregnancy was performed to assess whether chemodilution had a plausible effect on maternal outcomes. Cut off of 60% of planned chemotherapy courses during pregnancy was arbitrary chosen based on the median proportion of antenatal chemotherapy in this series. Clinical variables were reported descriptively (including number of missing values) for cases and controls and compared (if applicable for both groups) between cases and controls using exact test of Fisher (for binary variables), $\chi 2$-test (for categorical variables with more than 2 levels) or Wilcoxon test (for continuous variables). All reported *p*-values are two-sided and $p \leq 0.05$ was considered statistically significant and CI symmetrically span 95%. No adjustment for multiple comparisons was planned or performed for the subgroup analyses. All analyses were performed using the SAS statistical software package (version 9.4; SAS Institute, Cary, NC). Missing values of covariates were imputed once, using the method of chained equations making use of IVEware, in order not to lose power due to the missing values.[334]

Results

In total, 662 pregnant women treated with chemotherapy were recruited from GBG (n= 280) and INCIP (n=382) for analysis. Survival was compared with 2081 non-pregnant breast cancer patients (GBG n=885; MBC n=1196). Clinical characteristics are depicted in Table 1. Pregnant patients were more likely to have stage II breast cancer, grade 3 tumors, ER/PR negative tumors or triple-negative breast cancer.

Table 1: Clinical characteristics of study group

	Overall		Pregnant		Non-pregnant		
Characteristic	**No.**	**%**	**No.**	**%**	**No.**	**%**	**p-value**
No. of patients	*2743*		*662*		*2081*		
Year of diagnosis							
Median, range	2012, 2000-2019		2012, 2000-2019		2012, 2000-2019		0.674
Age (years)							
Median, range	37, 19-47		34, 22-47		38, 19-45		<.001
<=30 years	362	13.2	126	19.0	236	11.3	<.001
>30-35 years	724	26.4	277	41.8	447	21.5	
>35-40 years	1017	37.1	205	31.0	812	39.0	
>40 years	640	23.3	54	8.2	586	28.2	
missing	0		0		0		
Parity							
Median, range	1, 0-10		1, 0-7		1, 0-10		<.001
Nulliparous	715	32.0	225	37.4	490	30.1	<.001
Multiparous	1516	68.0	377	62.6	1139	69.9	
Missing	512		60		452		
Stage							
stage I	516	19.8	97	16.1	419	20.9	0.035
stage II	1486	57.0	361	60.1	1125	56.1	
stage III	603	23.1	143	23.8	460	23.0	
missing	138		61		77		
Histological tumor type							
Non-lobular	2581	95.2	634	96.9	1947	94.6	0.016
Lobular invasive	131	4.8	20	3.1	111	5.4	
missing	31		8		23		
Grading, dichotomized							
G1-2	928	35.1	159	26.0	769	37.8	<.001
G3	1718	64.9	453	74.0	1265	62.2	
missing	97		50		47		
HER2 status							
negative	1937	72.6	443	71.5	1494	73.0	0.472
positive	730	27.4	177	28.5	553	27.0	
missing	76		42		34		
Hormone receptor status							
both ER and PgR negative	1014	37.4	310	48.4	704	34.0	<.001
ER and/or PgR positive	1696	62.6	330	51.6	1366	66.0	
missing	33		22		11		
Biological subtype							
Luminal A-like (HER2-/HR+ grade 1-2)	586	22.2	83	13.7	503	24.8	<.001
Luminal B-like (HER2-/HR+ grade 3)	539	20.4	110	18.2	429	21.1	
TNBC	782	29.7	236	38.9	546	26.9	
HER2 positive	730	27.7	177	29.2	553	27.2	
missing	106		56		50		
Treatment setting							
Neo-adjuvant treatment	1083	39.5	255	38.5	828	39.8	<.001
Adjuvant treatment	1611	58.7	370	55.9	1241	59.6	
Neo-adjuvant and adjuvant treatment	49	1.8	37	5.6	12	0.6	
missing	0		0		0		
Chemotherapy							
Anthracycline	579	21.1	147	22.2	432	20.8	0.089
Anthracycline + taxane	1916	69.9	469	70.8	1447	69.5	
Non-standard chemotherapy	248	9.0	46	6.9	202	9.7	
missing	0		0		0		
Most radical breast surgery							
No breast surgery	8	0.3	4	0.7	4	0.2	0.003
BCS	1295	50.6	262	45.3	1033	52.2	
Mastectomy	1255	49.1	313	54.1	942	47.6	
missing	185		83		102		
Most radical axilla surgery							
No axilla surgery	47	1.8	12	2.1	35	1.7	0.143
SNB	921	35.4	224	38.6	697	34.5	

ALND	1633	62.8	344	59.3	1289	63.8
Missing	142		82		60	
Delay to initiate trastuzumab[a]						
Median, range (weeks)			17, 1-41			
Trimester of BC diagnosis						
Median, range (weeks)			17, 0-39			
1st(weeks 1-13)			216	33.3		
2nd(weeks 14-27)			337	52.0		
3rd (>28 weeks)			95	14.7		
missing			14			
Initiation chemotherapy during pregnancy						
Median, range (weeks)			23, 4-39			
<20 weeks			227	35.4		
20-30 weeks			318	49.6		
>30 weeks			96	15.0		
missing			21			
Proportion of cycles chemotherapy during pregnancy, %						
Median, range			60.0, 9.1-100			

Abbreviations: BC: breast cancer, ER: estrogen receptor, PR: progesterone receptor, HER2: Human Epidermal growth factor Receptor 2, TNBC: triple negative breast cancer, SNB: node biopsy, ALND: Axillar lymph node dissection

[a]Because not for all cases the date of first administration of trastuzumab was reported, we defined the delay to initiate with trastuzumab as interval between diagnosis and delivery (in weeks)

Treatment

Most pregnant women were diagnosed in the second trimester of pregnancy. In 44.1% of pregnant patients chemotherapy was initiated in a neo-adjuvant setting, compared to 40.4% in the non-pregnant group (p<0.001). Patients that received neo-adjuvant chemotherapy were diagnosed later in pregnancy and received a lower proportion of total chemotherapy during pregnancy compared to pregnant patients that received chemotherapy in the adjuvant setting (median 23 weeks vs 13 weeks, p<0.001 and 50% vs 75%, p<0.001, for pregnant and controls respectively). Pregnant patients received neo-adjuvant chemotherapy earlier following diagnosis compared to non-pregnant patients (median 15 days (range 0-134) vs 25 (0-177), p<0.001), whereas in adjuvant setting there was no difference in treatment delay between pregnant and non-pregnant patients (Table SIV-VII.1 and 2).

Table 2: Multivariable Cox proportional hazard regression

	No. pregnant	No. non-pregnant	Outcome	HR	95%CI	p-value
A. Total study group						
	662	2081	DFS	1.024[1]	0.824-1.273	0.830
			OS	1.082[1]	0.810-1.446	0.592
B. Pregnant patients treated with more than 60% of chemotherapy during pregnancy vs controls						
	339	2081	DFS	0.811[2]	0.618-1.064	0.130
			OS	0.848[2]	0.584 - 1.231	0.387
C. Pregnant group, for number of cycles given during pregnancy						
	654		DFS	0.941[3]	0.856-1.034	0.203
			OS	0.926[3]	0.817- 1.049	0.228
D. Pregnant group, by proportion of chemotherapy during pregnancy						
	645		DFS	0.956[4]	0.896-1.020	0.176
			OS	0.969[4]	0.889 - 1.057	0.479

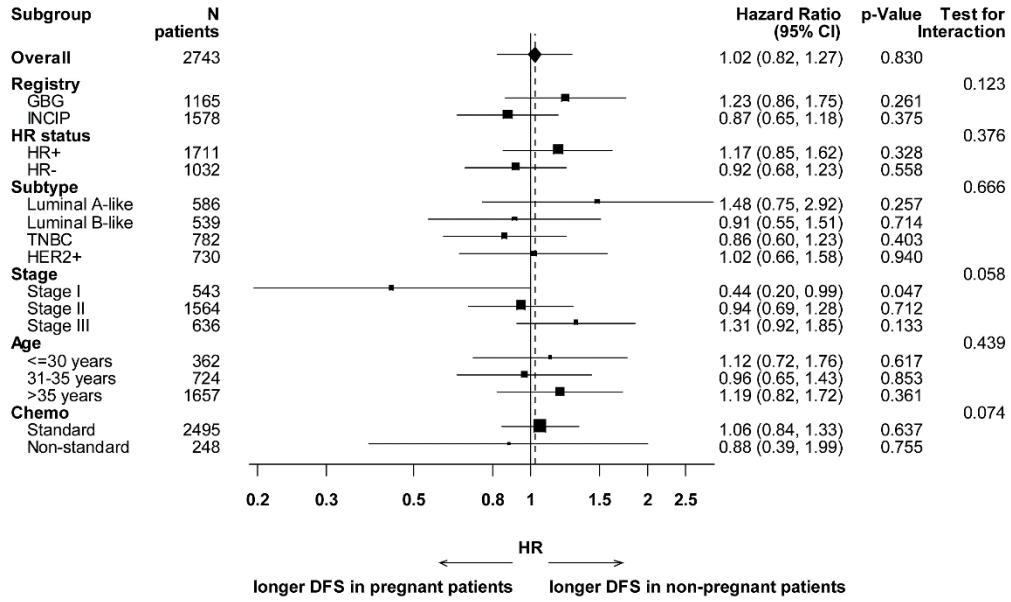
Multivariable cox proportional hazard regression for DFS and OS, adjusted for age, stage, grading, histology, hormone receptor status, HER2 status and type of chemotherapy.

**Distant disease-free survival (DDFS) was calculated from diagnosis to distant relapse or death.*

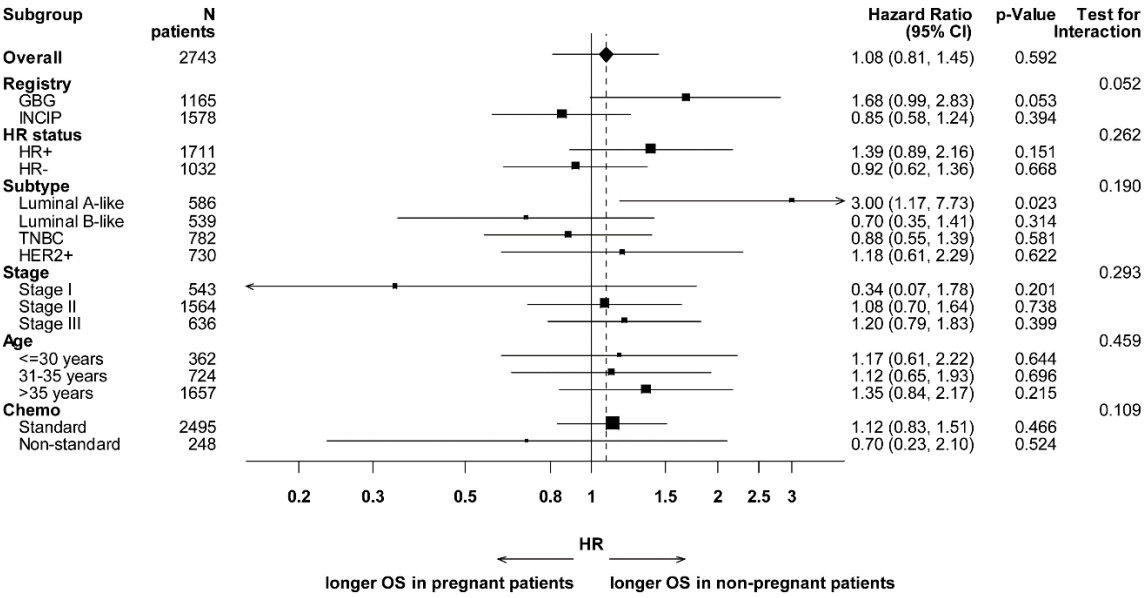
[1]HR for pregnant vs control; [2]HR for pregnant patients who received at least 60% of chemotherapy during pregnancy vs control; [3]HR per 1 cycle increment; [4]HR per 10% increment

Figure 1: Forest plots with results of multivariate Cox regression analysis of disease-free survival (DFS) (Figure 1a) and overall survival (OS) (Figure 1b) by subgroups of interests (registry, HR (hormone receptor) status, molecular subtype, stage of breast cancer, age at diagnosis, chemotherapy regimen as part of primary treatment (standard vs non-standard)

A. Disease-free survival



B. Overall survival



Survival

With a median follow-up of 66.3 months (51 months for pregnant women and 71 months for non-pregnant women), 87 (13.1%) pregnant women and 274 (13.2%) non-pregnant controls died (Figure SIV-VII.1). For pregnant patients, the observed 3 and 5-year DFS and OS was 78.0%, 73.2% and 90.3%, 84.2%, respectively. For non-pregnant patients the observed 3 and 5-year DFS and OS was 85.0%, 78.1% and 94.3%, 89.2%, respectively. Multivariable cox proportional hazard regression for DFS and OS, adjusted for age, stage, grading,

histology, hormone receptor status, HER2 status and type of chemotherapy, did not reveal a worse prognosis for pregnant patients compared to non-pregnant patients (HR 1.024 (0.824-1.273 *p*=0.830 for DFS and HR 1.082 (0.810-1.446), *p*=0.592 for OS) (Table 2). Multivariable analysis in the pregnant group revealed that the number of cycles or proportion of chemotherapy did not impact DFS or OS. Survival of pregnant patients that received more than 60% of the chemotherapy during pregnancy was similar to non-pregnant women. Further subgroup analysis did show comparable results per registry (GBG versus INCIP), hormone-receptor status, molecular subtype, stage, age (≤30 years) and chemotherapy (standard versus non-standard treatment) for both DFS and OS (Figure 1). However, for luminal A breast cancer, pregnant patients had worse OS compared with non-pregnant, whereas DFS was comparable.

Discussion

To date, this is the largest cohort comparing DFS and OS of women receiving chemotherapy for PrBC and non-pregnant young breast cancer patients. Survival of PrBC in general was comparable to controls, hereby emphasizing the results of our previous cohort that did not further explore the subgroup with antenatal chemotherapy.[138] In particular, we observed similar outcomes for women who received the majority (>60%) of chemotherapy during pregnancy compared to non-pregnant controls. Although the impact of gestational physiologic changes on the efficacy of chemotherapy is plausible and a concern, this is not reflected in this cohort. Hence, these results confirm current recommendations to treat pregnant patients as their non-pregnant counterparts, according to standard guidelines with gestation-related treatment adaptations.[4]

Recently, we have shown that for chemotherapeutic agents commonly used in breast cancer (doxorubicin, epirubicin, paclitaxel and docetaxel), decreased drug exposures were observed in pregnant patients.[353] Interestingly, an important inter-drug variation was observed. While pregnancy advances, albumin concentrations decrease and hepatic cytochrome p450 enzymes involved in the taxane metabolism increase, resulting in significant changes most importantly in taxane pharmacokinetics.[126] Indeed the gestation-related changes on chemotherapy concentrations appear to be more important for the highly protein bound taxanes, compared to anthracyclines, resulting in a 24.0% lower peak plasma concentration and 12% lower $AUC_{0\text{-}48h}$ for paclitaxel when compared to non-pregnant patients.[126,353] However, in our series, multivariable cox regression analysis did not reveal a negative prognostic effect of the use of taxanes. Since only a subgroup of the present cohort received taxanes, it is prudent to start whenever possible with anthracycline-based treatment during pregnancy, followed by taxanes (as in over 90% of pregnant patients in this series),.[356] Our results support the recommendation to dose chemotherapy based on the actual body weight of pregnant patients and there is no need to increase the dosage because of pregnancy.[4,126,353] The latter would likely raise maternal and fetal toxicity and risks, including fetal growth restriction and preterm delivery.[100]

When antenatal breast cancer treatment is considered, both short-and long-term concerns for the mother and the child-to-be are balanced. With close maternal-fetal surveillance following chemotherapy exposure, fetal and pediatric outcome after antenatal exposure to chemotherapy are reassuring, although a continuous follow-up of these children remains warranted.[40,113] The data we report now add to maternal safety. It is tempting to speculate that this finding can be extrapolated to other less frequent cancers. In a recent matched case control study including 124 pregnant patients with Hodgkin lymphoma, maternal outcome was also reassuring.[160]

As trastuzumab has the ability to cross the placenta and interferes with fetal renal function resulting in oligohydramnios and secondary lung dysplasia, its antenatal use should be avoided.[61] Trastuzumab treatment delay until after delivery appears not to impact survival in this series (data not shown). As the sequential use

of trastuzumab following chemotherapy is a clinically used alternative in non-pregnant breast cancer patients (eg. HERA (HERceptin Adjuvant) trial), the initiation of trastuzumab after delivery in PrBC can be justified in order not to put the fetus at risk.[357-359]

In contrast to our previous results, this larger cohort suggests a worse OS for pregnant women receiving chemotherapy for luminal A breast cancer compared to non-pregnant luminal A breast cancer controls. For the other breast cancer subtypes (including luminal B) our data reveal a similar survival for pregnant and non-pregnant women. However, focusing on subgroups further complicates data interpretation. The complex gestation-related hormonal interactions and associations with cancer development and progression are still incompletely understood.[124] Whether there exists a clinical genuine adverse effect of the high gestational estrogen levels on a hormone receptor positive tumor, as suggested in preclinical research, needs further research, with more detailed data including longer follow-up and pathological response following neo-adjuvant chemotherapy.[125]

Studying the prognosis of PrBC is challenging because of its rarity, the different diagnostic and treatment approaches within this international setting, as well as the multiple confounders and the large number of patients needed to achieve sufficient power. Although this study is the largest reporting on survival of patients receiving chemotherapy for PrBC, there are several limitations to consider. As 180 pregnant patients and 865 non-pregnant patients were also included in our previously published series, this cohort study is not an independent validation of our results.[138] A major limitation is the partial retrospective data collection, inevitably resulting in missing data; Available follow-up data of non-pregnant controls was 20 months longer compared to pregnant women. The retrospective design in an international collaboration results in a very heterogeneous selected population, staged and treated according to standard local policies. Furthermore, supplementary analyses of particular subgroups of interest are still underpowered. Data were not detailed regarding effective chemotherapy dosages, however we may assume that chemotherapy in this cohort was prescribed based on actual body weight, as participating centers are following current recommendations. A possible pregnancy-related delay to initiate hormonal treatment was not taken into account in this analysis, however most patients were diagnosed in the second half of pregnancy and were still receiving chemotherapy or surgery after delivery. Furthermore, data were too scarce to explore effects of double HER2 blockade or BMI or prognosis of subgroups according to histological subtype or treatment setting.

Conclusion

Prognosis of pregnant patients treated with chemotherapy is comparable to non-pregnant patients. Although gestational-induced alterations in chemotherapy concentrations are likely, these do not seem to affect maternal oncological safety. These results support initiation of standard chemotherapy for PrBC where indicated for oncological reasons at the same dosage as in non-pregnant patients.

Chapter VIII - Obstetric and maternal outcomes in patients diagnosed with Hodgkin lymphoma during pregnancy: a multicenter, retrospective, cohort study

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Abstract

Background

Outcomes for mother and child following Hodgkin lymphoma during pregnancy are underinvestigated. This retrospective cohort study of the International Network on Cancer, Infertility and Pregnancy (INCIP) reports the obstetric outcomes and maternal survival according to antenatal management.

Methods

Oncological and obstetric data of 134 pregnant patients diagnosed with HL between January 1, 1969 and August 1, 2018 were collected from the INCIP database. Obstetric outcomes of patients that received antenatal chemotherapy were compared to patients without antenatal treatment. Progression-free (PFS) and overall survival (OS) of 77 pregnant patients with early or advanced stage classical HL diagnosed since January 1, 1997, was compared to 211 non-pregnant, young (≤41 years) females with similar diagnostic and treatment characteristics, matched for stage and prognostic score and selected from databases of three tertiary centers.

Findings

Most patients were diagnosed with early stage HL (75%) and nodular sclerosis subtype (81%). 58% of patients initiated antenatal treatment and over the years chemotherapy was increasingly commenced during pregnancy. 90% of pregnancies ended in a live birth. 19% of neonates were small for gestational age and birthweight percentiles were lower in neonates prenatally exposed to chemotherapy compared to non-exposed neonates (p=0·035).

Survival of pregnant patients was not significantly different from non-pregnant controls. Five-year PFS and OS for early stage HL was 82·5% [95% CI 67·4;91·1] and 97·3% [82·3;99·6] for 62 pregnant patients and 88·3% [81·6;92·7] and 98·4% [93·6;99·6] for 142 controls, respectively [for PFS HR 1·80 (0·84;3·87), p=0·130; for OS HR 1·63 (0·35;7·65), p=0·534]. Subgroup analysis of patients with advanced stage HL and patients with early stage HL that received antenatal chemotherapy or had a pregnancy-related treatment delay was reassuring.

Interpretation

As maternal survival is reassuring, antenatal chemotherapy or a deferral of treatment until postpartum in well-selected cases can be considered, with regular obstetric follow-up to safeguard fetal growth.

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Introduction

Following the trend of increased maternal age, over time more patients are 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.[2,3] Hodgkin lymphoma (HL) represents the most common hematological malignancy, with an estimated incidence between 5 and 8 per 100,000 live births.[2,4]

Limited studies are available to guide the management of HL during pregnancy. El-Messidi published a cohort on 638 cases, revealing an increased risk of preterm delivery, postpartum blood transfusion and venous thrombosis but overall similar short-term maternal and neonatal morbidity and mortality compared to 7,916,388 controls.[4] In contrast, a Danish cohort study on 292 births showed reassuring birth outcomes without increased risk of preterm delivery, stillbirth or low birthweight (<2500 gram) at term.[5] Concerning antenatal treatment, most evidence exist on the use of ABVD (doxorubicin, bleomycin, vinblastine, dacarbazine), whereas experience with BEACOPP (bleomycin, etoposide, adriamycin, cyclophosphamide, vincristine, procarbazine, prednisone) is limited.[6,7] Some authors suggest deferral of treatment until after delivery to minimize fetal risks in early stage HL.[6] However, in symptomatic patients or advanced stage HL, immediate treatment might be indicated. Increased awareness of the feasibility of antenatal chemotherapy resulted in more patients receiving anticancer drugs.[3] 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 antenatal management in detail. [8-10] Survival of patients that initiate antenatal treatment is of great interest because gestational physiological changes (e.g. higher plasma volume and distribution volume, increased glomerular infiltration, altered hepatic metabolism) potentially affect pharmacokinetics, resulting in a lower plasma-drug exposure.[11] Whether this chemodilution affects the efficacy of chemotherapy remains questioned. Also, it is unclear if pregnancy-induced adaptations in management (e.g. deferral of treatment until the second trimester or postpartum) impact survival.

Here, we report the results of a multicenter collaboration that retrospectively collected clinical data of 134 pregnant patients with HL. The aim of this study is to assess management and obstetric outcome when HL is diagnosed during pregnancy. Also, the oncological maternal outcome is studied by assessing progression-free (PFS) and overall survival (OS) of pregnant patients diagnosed with classical HL 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) launched a registry for oncological and obstetric data of patients with a cancer diagnosed in association with

pregnancy. In total, 17 academic centers 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 patients with a diagnosis of pregnancy-associated HL between 1969 and 2018. 65 (49%) of 134 eligible patients were also included in a recent INCIP study on oncological management and obstetric outcome.[3] However, the study design precluded cancer-specific data analysis and thus no specific information on management and maternal outcomes for HL patients was reported. This study was approved by the Ethical Committee of University Hospital Leuven (Belgian number B322201421061) and approval and written informed consent was obtained when required by participating centers.

Procedures

Pregnant patients with a diagnosis of any histological subtype of Hodgkin lymphoma were included for analysis. Patients with a postpartum diagnosis, recurrence during pregnancy or missing data on oncological management and pregnancy outcome were excluded. Clinical data regarding diagnosis, treatment and outcomes for mother and child were collected. All patients were staged and treated according to local protocols. Due to the retrospective study design predefined definitions of remissions, recurrence or follow-up after treatment were not possible. A patient was considered to have a recurrence of HL if this was registered with details based on biopsies or imaging. HL stage was defined according to the Ann Arbor staging system as early stage (stage I-II) and advanced stage (stage III-IV).[12] 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 were used for prognostic scores.[13,14] All included patients initiated treatment within a year after diagnosis [maximum treatment delay was 232 days (one patient diagnosed with stage IIA (unfavorable) HL in first trimester of pregnancy, initiated ABVD treatment after term delivery)].

Outcomes

Twin pregnancies and stillbirths were excluded for descriptive analysis of obstetric outcome (gestational age at delivery, mode of delivery, onset of labor and reasons for planned delivery) and neonatal complications. The outcome (birthweight, obstetric complications, congenital malformations, neonatal complications and neonatal intensive care unit (NICU) admission) of chemotherapy-exposed neonates was compared with non-exposed neonates. Patients that exclusively received antenatal radiotherapy were reported separately. 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 (=customized birthweight percentile, GROW v.8.0.2, www.gestation.net). Congenital malformations were assessed for all live births or stillbirths according to Eurocat.[15]

To study the effect of pregnancy on maternal outcome, survival analysis was restricted to patients with similar tumor (classical HL; nodular sclerosis or mixed cellularity) and treatment (ABVD-based) characteristics. We

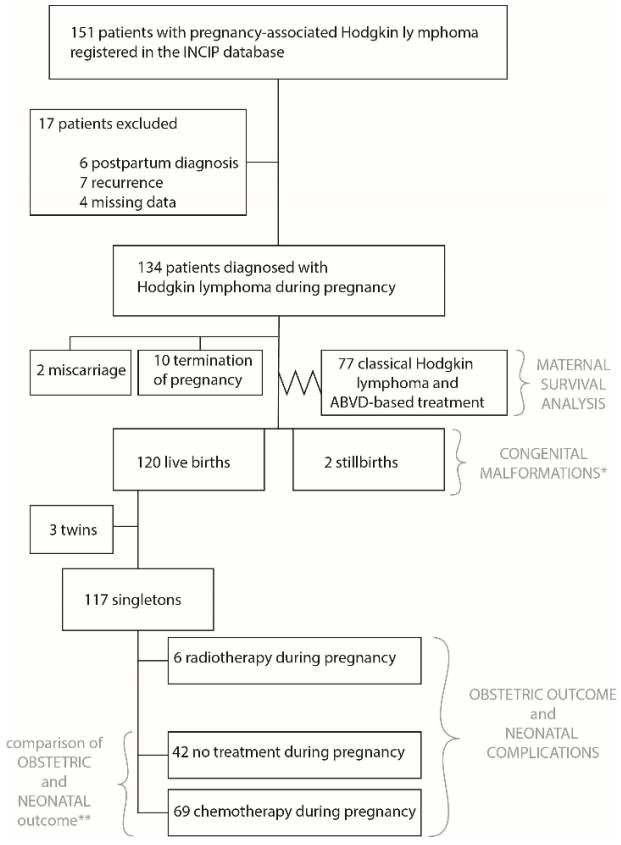
identified young (≤41 years) non-pregnant controls who were matched for stage and prognostic score at diagnosis with pregnant patients with ongoing pregnancies (patients with a termination of pregnancy or miscarriage were excluded). Missing data did not allow us to match for B symptoms or bulky disease. 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 hematology and oncology at the University Hospitals of Leuven (Belgium), the Erasmus MC Cancer Institute in Rotterdam and the University Medical Centers in Groningen (the Netherlands). Progression-free survival was calculated from the time of diagnosis to the time of disease relapse/progression or death. OS was measured from the date of diagnosis to the date of death of any cause.

Statistical analysis

Sample size calculation was not performed as the rarity of HL during pregnancy complicates the collection of cases, even retrospective. 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 (favorable versus non-favorable 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. Subgroup analyses for pregnant patients that initiated with ABVD and patients with a pregnancy-related treatment delay, arbitrary defined as a delay of more than 35 days since diagnosis, were performed. Low numbers did not allow further subgroup analysis for advanced stage disease. Exploratory analysis by linear regression aimed to investigate a dose response impact on customized birthweight percentile of neonates prenatally exposed to ABVD.

Besides descriptive statistics, we used the Fisher exact test to compare groups on binary variables and the independent t test or Mann Whitney U test, as appropriate for continuous variables. Two sided p values of 0·05 or less were considered significant. Data

Figure 1: Study scheme
**cfr. Table SIV-VIII.7*
*** Comparison of OBSTETRIC OUTCOME (birthweight, obstetric complications,) and NEONATAL OUTCOME (congenital malformations, neonatal complications, NICU admission) (cfr. Table 2 and Table SIV-VIII.4)*



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).

Results

134 pregnant patients with a diagnosis of HL were included (Figure 1). Median age at diagnosis was 27 years (IQR (Interquartile range) 24·0-32·0) (Table 1). The majority of patients were diagnosed with nodular sclerosis HL (109 of 134, 81%),had early stage HL (101 of 134, 75%), were nulliparous (87 of 134, 65%) and had no B symptoms at diagnosis (at least 74 of 134, 55%).

Table 1: Clinical characteristics, management and outcome of patients with Hodgkin lymphoma during pregnancy (n=134)

Characteristics	Total N.	N. of patients	%
Age (years) at diagnosis	134		
<25		42	31
25-29		38	28
30-34		39	29
≥35		15	12
Gestational age at diagnosis	134		
First trimester		26	19
Second trimester		82	61
Third trimester		26	19
Hodgkin lymphoma, subtype*	134		
Nodular sclerosis		109	81
Mixed cellularity		8	6
Lymphocyte rich		4	3
Nodular lymphocyte pre-dominant		1	1
NA		12	9
Prior Pregnancies	134		
Nulliparous		87	65
1		33	25
>1		13	9
NA		1	1
Ann Arbor Stage	134		
I		12	9
II		89	66
III		17	13
IV		14	11
NA		2	1
B-symptoms	134		
Yes		22	16
No		74	55
NA		38	28
Bulky disease	134		
Yes		6	4
No		92	69
NA		36	27
EORTC prognostic groups for early stage	101		
Favorable		41	40
Unfavorable		25	25
NA		35	35
IPS for advanced stage	31		
0		4	13
1		5	16
2		4	13
≥3		9	29
NA		9	29

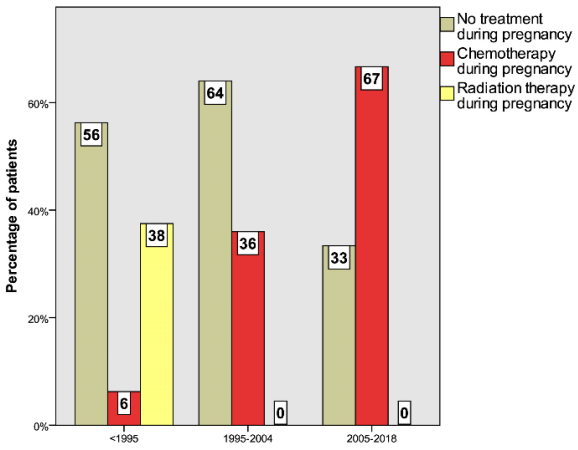
Management during pregnancy	134		
No treatment		56	42
Termination of pregnancy		*10*	*16*
Miscarriage		*2*	*4*
Deferred treatment until after delivery		*44*	*80*
Chemotherapy		72	54
Chemotherapy and radiation therapy		*1*	*1*
Radiation therapy		6	4
Pregnancy outcome	134		
Live birth		120	90
Still birth		2(1 congenital syndrome)	1.5
Miscarriage		2(16 and 17 weeks GA)	1.5
Termination of pregnancy		10	7
Follow-up of patients	134		
Complete remission		97	72
Alive with Recurrent disease		10	7
Deceased		12	9
Death of disease		8	67
Death of secondary cancer (post-radiation)		4	33
Lost in follow-up		15	11

*WHO classification, 2008. Abbreviations: EORTC, European organization of Research and Treatment of Cancer; IPS, International prognostic score; NA not applicable; GA, Gestational Age

Median gestational age at diagnosis was 20 weeks (IQR 14·8-27·0). The management of HL according to trimester of pregnancy at diagnosis is shown in Figure SIV-VIII.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). ABVD (at standard doses) was the most common regimen (66 of 72, 92%) (Table SIV-VIII.1). An overview of six patients that received only radiotherapy during pregnancy is given in Table SIV-VIII.2.

In total, 120 (90%) of 134 pregnancies ended in a live birth. Ten patients, diagnosed in first half of pregnancy opted for a termination of pregnancy, four of whom had advanced stage disease. One fetus with a congenital syndrome (exact diagnosis not registered) deceased at 24 weeks of gestation, soon after administration of ABVD. In one patient a stillbirth with a placental hematoma was detected at 31 weeks of gestation, after three cycles of ABVD. Two patients presented with a miscarriage before the initiation of treatment. Median gestational age at birth for all 117 singletons was 37 weeks (IQR 35·8-38·6) (Table SIV-VIII.3). Therapy planning was the most important reason for preterm planned delivery (23 of 36, 64%). Patients receiving antenatal therapy had more obstetric complications, the most common being preterm contractions and preterm rupture of membranes (Table SIV-VIII.3-5).

Figure 2: Evolution of management over time



In total, 123 children were born out of 122 ongoing pregnancies (two stillbirths, three twin pregnancies and 117 singletons). The incidence of SGA neonates was not

significantly different for chemotherapy-exposed neonates (15 of 69, 22%) compared to non-exposed neonates (6 of 42, 16%) (p=0·455, Table 2). However, the distribution of customized birthweight percentiles differed significantly between both groups (p= 0·035, see Figure SIV-VIII.2). Patients that initiated antenatal chemotherapy were diagnosed at an earlier gestational age and had a longer interval between diagnosis and delivery, compared to patients that initiated treatment postpartum (p<0·0001). Linear regression analysis revealed that the duration of prenatal exposure to ABVD was negatively associated with customized birthweight percentiles (Table SIV-VIII.6).

Table 2: Obstetric characteristics and neonatal outcome of singletons born from patients with Hodgkin Lymphoma (n=111), prenatally exposed to chemotherapy (n=69) or without prenatal cancer treatment exposure (n=42)*

Neonatal outcome	Total		Chemotherapy during pregnancy (n=69)		No antenatal therapy (n=42)		p-value
	N.	%	N.	%	No	%	
Gestational age at diagnosis (weeks)							<0.0001 *(Δ)*
- 2.0-12.9	11	10	9	13	2	5	
- 13.0-27-.9	75	68	56	81	19	45	
- 28.0-41.0	25	22	4	6	21	50	
Interval between diagnosis and delivery (weeks)							<0.0001 *(Δ)*
- 0-9.9	34	31	7	10	27	64	
- 10.0-19.9	45	41	35	51	10	24	
- 20.0-29.9	30	27	25	36	5	12	
- >30.0	2	1	2	3	0	0	
Gestational age at delivery (weeks)							0.138 *(Δ)*
28.0-31.9	3	3	2	3	1	2	
32.0-33.9	7	6	2	3	5	12	
34.0-36.9	35	32	20	29	15	36	
37.0-41.0	66	59	45	65	21	50	
Birthweight (gram)**							0.608 *(Δ)*
- <2500	32	30	21	31	11	30	
- 2500-2999	36	34	25	37	11	30	
- 3000-4000	35	33	21	31	14	38	
- >4000	2	2	1	1	1	3	
- unknown	6		1		5		
Customized Birthweight Percentile							0.035 *(Δ)*
- <P10	21	20	15	22	6	16	
- P10-P24	28	26	23	34	5	14	
- P25-P49	24	23	13	19	11	30	
- P50-P74	13	12	8	12	4	11	
- P74-P90	11	10	4	6	7	19	
- >P90	9	9	5	7	4	11	
- unknown	6		1		5		
Small for gestational age (<P10)***	21	20	15	22	6	16	0.455 *(ǂ)*
Major congenital malformations							
Yes	3	3	2	3	1	3	0.409 *(ǂ)*
No	102	97	64	97	38	97	
Unknown	6		3		3		
Major neonatal complications****							0.406 *(ǂ)*
Yes	6	6	3	5	3	7	
No	94	94	63	95	36	93	
Unknown	11		3		3		
NICU admission							0.504 *(ǂ)*
Yes	31	31	19	29	12	35	
No	69	69	47	71	22	65	
Unknown	11		3		8		

* Analysis of all singleton live births (six neonates prenatally exclusively exposed to radiation therapy excluded and three twin pregnancies excluded).
** Chemotherapy: median 2780 gram (range 1608-4423); No antenatal treatment median 2800 gram (range 1560-4276)
*** Small for gestational age: neonate with a birthweight that is below the 10th (customized) percentile.
**** respiratory distress and neonatal jaundice related to prematurity excluded
(Δ) Mann–Whitney U test; (ǂ) Fisher exact test

Four (3%) of 123 children had a major congenital anomaly at birth (two cases of syndactyly, one atrial septal defect and one congenital syndrome, Table SIV-VIII.7). Four children (3%) had minor physical abnormalities. Myelosuppression (leukopenia, anemia) was reported in two fetuses, born one and two weeks after the last administration of chemotherapy (Table SIV-VIII.8). In total 32 (31%) of 123 children were hospitalized at birth and prematurity was the main reason (21 of 32, 66%). Other reasons for admission were dysmaturity (5 of 32, 16%) or observation (6 of 32, 19%). Two twin pregnancies ended by caesarean section at 29 weeks of gestation due to preterm labor within two weeks following chemotherapy. Another patient delivered of twins at 35 weeks, following induction of labor. The twins were healthy at birth but hospitalized for prematurity.

Table 3: Results of survival analysis for early stage, treatment subgroups for early stage and advanced stage HL

	Number of events/ Total number of patients (%)	5-year PFS (%) (95% CI)	Hazard ratio (95% CI)	P-value	Number of events/Total number of patients(%)	5-year OS (%) (95% CI)	HR (95% CI)	P-value*
Early stage HL (all)								
Pregnant	10/62 (16)	82·6 (67·4;91·1)	1·80 (0·84;3·87)	0·130	2/62 (3)	97.3 (82·3;99·6)	1·63 (0·35;7·65)	0·534
Non-pregnant	16/142 (11)	88·3 (81·6;92·7)			7/142 (5)	98.4 (93·6;99·6)		
Early stage HI, subgroup that initiated chemotherapy during pregnancy								
Pregnant	8/45 (18)	78·3 (58·8;89·3)	1·948 (0·90;4·20)	0·089	1/45 (2)	96·2 (75·7;99·5)	0·83 (0·12;5·92)	0·854
Non-pregnant	12/104 (12)	87·8 (79·5;89·0)			7/104 (6)	97·7 (91·2;99·4)		
Early Stage HL, subgroup with pregnancy-related delay of treatment (>35 days between diagnosis and initiation treatment)								
Pregnant	3/21 (14)	88·0 (59·4;96·0)	2·286 (0·24;22·26)	0·477	0/21 (0)	100 (.;.)	NA**	NA**
Non-pregnant	3/33 (9)	90·9 (74·4;97·0)			0/33 (0)	100 (.;.)		
Advanced Stage HL (all)								
Pregnant	1/15 (7)	90·9 (50·8;98·7)	0·36 (0·04;2·90)	0·334	0/15 (0)	100 (.;.)	NA***	0·146
Non-pregnant	16/69 (23)	74·0 (60·9;83·3)			4/69 (6)	96·2 (85·5;99·1)		

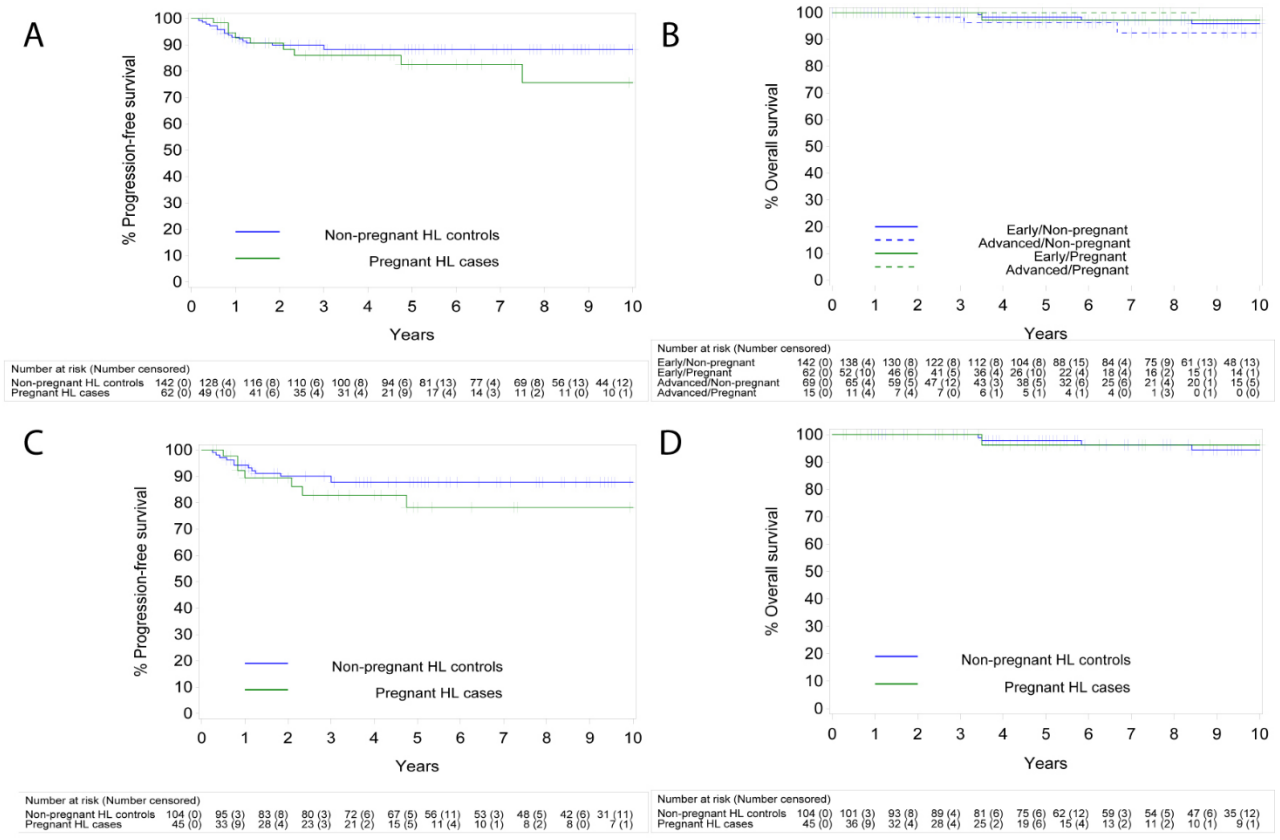
Abbreviations: 95% CI, 95% Confidence Interval; PFS, Progression-free Survival; OS, Overall Survival; HR: Hazard Ratio; HL Hodgkin lymphoma
* P-value from Cox regression using a robust sandwich estimate of Lin and Wei (1989) to account for clustering due to matching and corrected for age
** HR and p-value could not be estimated as no events occurred in both groups
*** P-value from Cox regression using a robust sandwich estimate of Lin and Wei (1989) to account for clustering due to matching; P-value based on Score test, no correction for age, HR cannot be estimated

In total 211 matched control patients were selected for 77 pregnant patients that received ABVD-based treatment for classical HL. For six excluded cases with early stage HL no matched controls were found. Six included patients with early stage and unknown prognostic scores were matched to six early stage control patients with unknown prognostic score. These cases had excellent survival without any events. Diagnostic year and use of radiotherapy in primary treatment did not differ between pregnant and non-pregnant cases (Table SIV-VIII.9).

The median follow-up of pregnant patients was 54·5 months (IQR 17·0-92·0). Survival for early and advanced stage HL was not significantly different for pregnant patients compared to corresponding controls (Table 3). Five-year progression-free survival and five-year overall survival for early stage HL, was 82·6% [95% CI

67·4;91·1] and 97·3% [95% CI 82·3;99·6] for pregnant patients and 88·2% [95% CI 81·6;92·7] and 98·4% [95% CI 93·6;99·6] for non-pregnant controls, respectively (Figure 3A and B). For advanced stage HL, 5-year progression-free survival and overall survival was excellent, respectively 90·9% [95% CI 50·8;98·7] and 100% for 15 pregnant patients and 74·0% [95% CI 60·9;83·3] and 96·2% [95% CI 85·5;99·1] for 69 corresponding controls. Subgroup analysis of 45 early stage HL pregnant patients that initiated antenatal chemotherapy revealed similar survival compared to non-pregnant controls [HR 1·948 (95% CI 0·90;4·20), p=0.089 for PFS and HR 0·83 (95% CI 0·12;5·92), p=0·854 for OS] (see Figure 3C and D). Early stage HL patients (n=21) with a pregnancy-related delay in initiation of treatment had no differences in survival compared to their controls (n=33) [HR 2·286 (95% CI 0·24;22·26), p=0·477 for PFS and no events in both groups for OS] (Figure SIV-VIII.3). In this group, more than half of patients (11 of 21, 52%) were diagnosed in the second half of pregnancy with stage I-II HL and initiated therapy postpartum whereas ten (48%) patients were diagnosed in early pregnancy and had a delay to initiate chemotherapy in the second trimester of pregnancy.

Figure 3: Survival of Hodgkin Lymphoma during pregnancy compared to matched controls



The 10-year progression-free (PFS) for early stage HL and overall survival (OS) for early and advanced stage HL of all pregnat patients and corresponding controles (3A and 3B) and the PFS and OS of the subgroup of pregnant early stage HL patients that initiated ABVD and corresponding controls (3C and 3D)

The PFS in 62 pregnant patients compared to 142 matched non-pregnant patients. (HR 1·80 (0·84;3·87), p=0·130) ***(B)*** *OS of 62 pregnant patients with early stage HL and 15 pregnant patients with advanced stage HL, compared to non-pregnant controls. (Early: HR 1·63 (0·35;7·65), p=0·534 Advanced: HR not calculable p=0·146)* ***(C)*** *PFS of 45 patients that initiated ABVD during pregnancy compared to 104 non-pregnant controls (HR 1·948 (0·90;4·20), p=0·0886).* ***(D)*** *OS of 45 patients that initiated ABVD during pregnancy compared to 104 non-pregnant controls (HR 0·83 (0·12;5·92), p=0·854).*

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 puts the foetus at risk for impaired growth. Survival of pregnant patients was not significantly different from non-pregnant controls. To our knowledge this is the largest series of HL during pregnancy reporting on obstetric outcome and maternal survival with detailed information on treatment modalities. 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 Hodgkin lymphoma.[8,9]

In the pre-chemotherapy era, extended field radiotherapy (e.g. mantle field) was the primary treatment for early stage disease, associated with a higher risk for cardiopulmonary toxicity and secondary malignancies.[16] Following the introduction of polychemotherapy regimens, current management of HL has evolved to combined-modality treatment, based on ABVD with or without subsequent radiotherapy.[17,18] In some countries (e.g. Germany) BEACOPP is the preferred regimen in advanced stage disease.[19] Radiation therapy, if indicated, shifted from extended field to more targeted "detectable nodal" irradiation techniques with less toxicities.[20] Data on antenatal radiation are based on small series, but irradiation of supra-diaphragmatic disease appears to be associated with a low risk for the foetus.[21] While the option of radiotherapy during pregnancy can be considered in well selected cases, the treatment for HL nowadays is initially chemotherapy-based.[17,18] The evolution of management is reflected in this series, with more patients initiating antenatal chemotherapy over time and less patients receiving radiation therapy.

The overall obstetric complication rate was higher in patients receiving antenatal treatment compared to patients without antenatal treatment, explained by the higher incidence of preterm contractions. Another series on 44 pregnant patients with chemotherapy for early stage HL reported 22% preterm delivery, but no other obstetric complications.[7] 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.[22] In this cohort, 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%).[23] More than one third of patients had an induction of labor, which is also higher than the international reported data (9·6 to 25%).[24]

In studies on obstetric outcome it is important to assess birthweight percentiles, that correct for gestational age at delivery, as it enables to identify SGA neonates. These neonates most likely did not reach their growth potential and are at risk of adverse perinatal outcomes. As customized birthweight percentiles were significantly lower for neonates prenatally exposed to chemotherapy compared to non-exposed neonates, we

conclude that antenatal chemotherapy might impact fetal growth, as already demonstrated in former studies.[3,25] Other studies on HL focused on the absolute birthweights of neonates, not correcting for gestational age at delivery, or were too small to draw conclusions.[5,8] Although exploratory analyses (without correction for confounders) in this study revealed a dose response impact on birthweight percentiles, this is a topic of ongoing research as in a cancer population not only chemotherapy, but also disease activity, malnutrition, and maternal stress might explain impaired fetal growth. The high overall incidence of SGA of 19% in this series supports this multifactorial cause. In addition, patients that initiated antenatal chemotherapy were significantly more frequently diagnosed in early pregnancy with longer intervals between diagnosis and delivery, compared to patients that initiated treatment postpartum. These patients are thus subject to a longer antenatal period of cancer-related disease activity, complaints and stress, which might also contribute to impaired fetal growth.

This series did not find an increased neonatal morbidity, consistent with prior data.[5,7,8] 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.[26,27]

In the literature of the non-pregnant population 5 year progression-free survival ranges between 86·4 and 94·2% and 5 year overall survival between 96·0 and 98·8% for early stage HL.[28] The survival of patients with advanced stage HL is inferior with reported rates of 78% 5 years progression-free survival and 90% 5 year overall survival.[29] Thus, survival rates from the non-pregnant matched control group in this study were within expectations.

Previous reports on maternal outcome after HL do no distinct between early and advanced stage HL, but similar survival rates were found.[9,10] One cohort study of 50 patients revealed a 3-year progression-free and overall survival of 85% and 97%, respectively.[8] A recent report on 44 patients diagnosed with early stage HL during pregnancy with median follow-up of 11·5 years revealed an overall survival of 95%, whereas our series found an overall survival of 98% at 10 years in this subgroup.[7]

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.[11] Currently it is recommended to define treatment dosages based on actual body weight, with (usually) increasing dosages as pregnancy advances.[11] Our data on overall survival show that, if HL relapse occurs after primary treatment with antenatal chemotherapy, 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 chemotherapy until the second trimester of pregnancy or postpartum. Maternal outcome in this series supports previous suggestions that in selected patients delivery can be expedited and therapy started postpartum, bridging with steroids or

vinblastine if appropriate.[6,8] 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]

An important strength of this study is the large cohort with detailed information on antenatal treatment modalities. As ABVD-based treatment for HL is still considered the standard treatment, the wide study period for survival is justified. An important limitation of this study is its retrospective design, resulting in missing data and a potential underreporting of complications. Matching based on age was not possible due to the rarity of cases, however survival analysis were limited to young women (≤41 years) and we corrected for age as a covariate., survival data should be interpreted carefully as we were unable to match for prognostic factors such as B symptoms and bulky disease and relapses after pregnancy were not always reported to be histologically confirmed. 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 used for staging during pregnancy. She was considered to have a relapse and aggressive treatment was initiated, in order not to risk undertreatment. Moreover, given the risk of late treatment-related toxicity, there has been an important evolution towards tailoring HL treatment according to treatment response assessed by interim Positron Emission Tomography (PET) scan results. Also, new irradiation techniques allow a better control of tumor sites.[20] Obviously, during pregnancy concerns on fetal radiation exposure limit imaging and radiation treatment options, which might lead to inferior staging and response evaluation. This is an important limitation of this cohort as a substantial amount of non-pregnant patients was managed according to this novel approach. The international character of the study inevitably results in selection bias and potentially involves differences in staging and treatment modalities influencing survival. However, all patients were treated in tertiary centers with high standards of care. Unfortunately country-based selection was not possible as most participating centers did not keep records routinely.

Specialists are encouraged to participate in the INCIP registry, as prospective research on maternal survival and the impact of cancer and cancer treatment on fetal growth is necessary.

Conclusion

In conclusion, data from this cohort suggest that ABVD during pregnancy for Hodgkin lymphoma does not affect maternal survival, but however might affect fetal growth, emphasizing regular obstetric follow-up in this high-risk population.

Part V - GENERAL DISCUSSION AND CONCLUSION

Reassuring case reports and case series on obstetric and neonatal outcomes following cancer treatment during pregnancy, resulted in increasingly more women receiving chemotherapy during pregnancy. Over the years this practice resulted in less terminations of pregnancy and more live births.[100] Hence, as clinical trials are practically not possible in this rare population of high risk pregnant women, questions remain on the best practice of care and the maternal and neonatal outcomes on a large scale. In this thesis we attempted to provide more evidence-based recommendations for clinicians, patients and their families on best treatment and follow-up schedules.

The duality by conflicting interests between mother and child which is felt by all caregivers involved in the treatment of pregnant women with cancer, is translated in the structure of this PhD. In the first 2 parts the obstetric outcome is described. Part 1 describes the obstetric outcome for all patients registered in the INCIP database, including sub-analyses per tumor type (Hodgkin lymphoma, non-Hodgkin lymphoma, leukemia, urological cancers and gastric cancer) and the impact of oncological surgery, exposure to G-CSF, and timing of chemotherapy. Part 2 is dedicated to fetal growth restriction. In the 3rd part the maternal outcome for the group of women with breast cancer and for the group with Hodgkin lymphoma is compared to non-pregnant women, accounting for oncological prognostic factors.

In summary, in this PhD observational data on obstetric and neonatal outcomes of registered pregnant women with Hodgkin lymphoma, non-Hodgkin lymphoma, urological cancers and gastric cancer were published to guide physicians in clinical management (chapter 2). This thesis builds further on the evidence that chemotherapy during pregnancy does not induce congenital malformations, as long as it is administered after 12 weeks of gestation (chapter 3). We observed the outcomes of women with oncological surgery and G-CSF during pregnancy (chapter 4 and 5). Overall, women with cancer are at risk of preterm onset of labor, preterm delivery and fetal growth restriction (chapter 1 and 6). The administration of antenatal chemotherapy even more increases the risk. A term delivery is encouraged in this population, to assure an optimal outcome for the child, as prematurity is a major risk factor for impaired neurocognitive outcome.[40] As a counterpart, while awaiting term delivery in this high risk population, there is an increased risk of preterm onset of labor. Other risk factors identified in this thesis for preterm onset of labor is metastatic and hematological disease (chapter 1). Preterm delivery is more frequently seen in women with hematological cancers. For fetal growth, cancer stage (metastatic disease), cancer type (hematological cancer), maternal weight gain during pregnancy, maternal hypertension and smoking play a role. Gestational age at cancer diagnosis is strongly related to birthweight percentiles. In this thesis, we revealed that there appears to be a direct dose-response effect of chemotherapy on neonatal birthweight (chapter 1). Through the collection of detailed follow-up data of pregnant women with cancer and the selection of pre-menopausal women with cancer outside of a pregnancy, we were able to study maternal prognosis in-depth. This thesis confirms that overall maternal prognosis in breast cancer and Hodgkin lymphoma appears unaffected by pregnancy, also when chemotherapy is given

during pregnancy (chapter 7 and 8). Results of this thesis support the current clinical practice of treating pregnant women with cancer by the standards of care recommended for non-pregnant women as much as possible. However, results should also increase the awareness of the multiple risk factors inherent to women with cancer. We encourage the management of these patients in specialized centers with a high-risk obstetrical and neonatal unit, with an expertise in a diagnosis of cancer during pregnancy and an holistic approach to cancer in pregnancy, including oncological, obstetric, psychological and nutritional risks

Identification of prognostic factors for adverse obstetric outcomes in women with cancer

During the course of this PhD the numbers of women with cancer during pregnancy registered in INCIP almost doubled. Larger numbers of data enabled us to further explore in-depth prognostic factors in the pregnant cancer population that contribute to adverse obstetric outcomes (chapter 1). As chemotherapy was assessed as a major risk factors for preterm spontaneous labor and SGA in previous INCIP analysis, we corrected for this in the analyses of this PhD project.[100] Of note, unfortunately in this chapter we were not able to make the distinguish between small for gestational age (SGA) neonates, assessed by neonatal birthweight, and fetal growth restriction fetuses, assessed by prenatal ultrasound. The ancient database did not incorporate reliable data on prenatal fetal growth, hampering the exploration of fetal growth restriction (FGR) in the final INCIP analyses of all cases in this PhD. We explored this important obstetric information in a detailed subgroup analyses (see comments on chapter 6).

First, we were able to explore the effect of cancer types, using breast cancer as a reference as this is the most common diagnosed cancer in pregnancy registered in INCIP. The risk of maternal death is significantly more in women diagnosed with gastro-intestinal cancer, leukemia, brain tumor and melanoma. Pregnancy loss was more frequently seen in leukemia, gastro-intestinal cancer and lymphoma. Preterm spontaneous labor occurred more frequently in women with leukemia and lymphoma, whereas the risk of spontaneous preterm delivery was only increased in leukemia patients. Women with gastro-intestinal and cervical cancer were more likely to have an elective preterm delivery. SGA was more common in women with leukemia. Cancer types with the lowest risks for adverse obstetric outcomes compared to breast cancer were borderline ovarian tumors, melanoma and thyroid cancer.

Second, by larger numbers we could separately investigate the impact of metastatic disease and leukemia, which were analyzed together as 'systemic disease (=TNM or FIGO stage IV, excluding brain tumors, and leukemia)' in previous analyses.[100] Leukemia in pregnancy was more likely to result in pregnancy loss, preterm spontaneous labor and SGA, while metastatic disease was more likely to result in maternal death and preterm elective delivery. Chemotherapy in pregnancy was a risk factor for all explored obstetric outcomes, except for maternal death, cesarean section and pregnancy loss. The latter needs some clarification. In this PhD analyses, pregnancy loss included miscarriages and stillbirths, excluding pregnancy terminations. It is well established

that chemotherapy exposure in first trimester of pregnancy has a high risk of fetal malformations and miscarriages.[39] The majority of women registered by INCIP was initiated with chemotherapy in the second trimester of pregnancy, explaining why the association of chemotherapy and early pregnancy loss was not found in this series. Data are reassuring concerning the association between chemotherapy and late pregnancy loss (stillbirth).

The difference in fetal effects of chemotherapeutic agents is explained by the different pharmacokinetic features resulting in differences in transplacental passage. Platina generally pass the placenta better compared to other agents.[360] The placental transfer of taxanes is low, however tissue binding is high resulting in a longer fetal drug exposure.[49] We confirmed that platinum agents and taxanes, as well as antimetabolites were strongly related to SGA. Our data now confirmed our hypothesis and clinical experience that chemotherapy induces preterm spontaneous labor (whereas the data of 2018 were not empowered enough to reach significance), with significant odds ratio's for all chemotherapy agents, except antimetabolites. Platinum agents were strongly associated with elective preterm delivery. Platina are mostly administered in women with gynecological cancers or locally advanced breast cancer, who are likely to have a planned early delivery for medical or oncological reasons. As in previous analysis, the use of taxanes, but also platinum agents and antimetabolites in pregnancy was associated with NICU admission. The high incidence of NICU admission is explained by preterm delivery and SGA (or fetal growth restricted) neonates in pregnant cancer patients.

Previous interim-analysis revealed a lower risk of NICU admission in women who received abdominal or cervical surgery in pregnancy. We could not confirm this finding, however found that this type of surgery reduces the risk of spontaneous preterm delivery. The majority of women who received abdominal surgery in pregnancy were diagnosed with borderline ovarian tumors and delivered term. Of note, one should realize that in the previous analyses outcomes are compared to women 'without surgery', however with cancer and thus with possible other inherent risk factors for preterm delivery, such as metastatic or hematological cancer, and invasive (eg. chemotherapy) cancer treatment. In this updated analysis, we compared outcomes with women who received extra-abdominal (mainly breast and excision of skin cancer) surgery.

Targeted or immunomodulatory treatment in pregnancy was a risk factor for preterm spontaneous labor, spontaneous preterm delivery and SGA. A higher maternal age increased the risk of delivery by cesarean section. Radiotherapy and low maternal weight gain, although low numbers, was not associated with any adverse outcome.

The literature remains controversial on the association of cancer and small for gestational age (SGA) neonates. The main reason for this is the use of different definitions (SGA, FGR, low birthweight) and different study populations (population-based or cohort with selection bias, different cancer types, antenatal management, low numbers of chemotherapy exposed cases). Many population-based studies cannot confirm that cancer

itself has a direct impact on SGA[12,15,17,19,24-29,79,92,93], while other studies do confirm an association with low birthweight (<2500g)[15-17,23,30,31,35] or SGA[12,18,21]. Population-based studies often lack information on antenatal management and only few reveal an association between antenatal chemotherapy and low birthweight[16,17] or SGA[12]. Some cohort studies confirm an association of antenatal chemotherapy with SGA[53,100,145], while others only reveal an association of chemotherapy with lower birthweights[98]. Indeed, low birthweight is often associated with cancer or chemotherapy in these studies because of the high rate of prematurity in the studied population. Of note, many population-based studies do not allow to elucidate the timing of cancer diagnosis and if or when chemotherapy was initiated. Also, in many studies the method of selection of cases of SGA or FGR is not clarified and we may wonder if in these database linkage studies there isn't an important registration bias with underreporting of cases. Nevertheless, it should be acknowledged that not only antenatal treatment but also other risk factors in the pregnant cancer population can impact fetal growth, complicating the research that tries to unravel associations.

Since 1996 there is a steep increase of women receiving chemotherapy during pregnancy, whereas during the last years we rather see a stabilization (55% in period 2016-2021 versus 52% in period 2010-2015 versus 33% in period 1996-2004). Probably we are at the limit of amount of women requiring chemotherapy for cancer and these numbers won't increase any longer. In contrast, we see a decrease in surgery during pregnancy (31% in period 2016-2021 versus 40% in period 2010-2015). This might be explained by the recommendation of neo-adjuvant chemotherapy prior to surgery in locally advanced breast cancer, the most common cancer stage seen in pregnant women.[4,361] The administration of radiotherapy and targeted therapy remains rather stable over the last years. This results from a careful decision-making as safety evidence is still scarce and these strategies have the potential to incorporate great risks for the unborn child.

Ideally, the analyses of chapter 1 should have been performed by comparing obstetric outcomes with non-cancer control patients. However, INCIP has no population-based design and relies on registration of cases by physicians from tertiary centers. The database is subject to a major selection bias and creating a pool of non-cancer controls in this international dataset would have been an enormous, maybe impossible, challenge. The strength of the INCIP database is its detailed data on antenatal management, what is often lacking in large population-based or nationwide trials. Hereby, INCIP can explore the impact on obstetric and neonatal outcomes of different treatment regimens in detail, a privilege that other databases do not have. An important disadvantage of a mainly retrospective dataset is the missing data. Prior to data analysis missing data were requested from INCIP members. For univariable analyses, the large numbers enabled us to use all available cases. In multivariable analysis we dealt with missing data by multiple imputation (chapter I).

Fetal growth in women with cancer

Ideally, to study fetal growth, prenatal scan data should be analyzed to identify 'pathological' fetal growth restriction (FGR). This is the first time in the literature that prenatal scan data of pregnant women with cancer was reviewed (chapter 6). The rarity of cancer and pregnancy complicates data collection on a scale large enough to draw conclusions. The collaboration with Elyce Cardonick, obstetrician in Cooper university hospital, as well as the initiative to perform serial ultrasound scanning in women who presented in the university hospitals of Leuven, enabled us to collect this information. From the analysis, we learned that FGR is common in pregnant women with cancer, and is most likely underestimated in studies that lack prenatal scan data. Antenatal chemotherapy appears to have a direct impact on fetal growth and neonatal birth weight. Both maternal as fetal Doppler studies in the pregnant cancer population are within normal limits, suggesting that FGR in the pregnant population is not the result from the conventional mechanism that affects the spiral arteries of the placenta. We believe that cytotoxic treatment directly affects the fast dividing cells in the developing fetus and placenta, resulting in an overall, symmetrical growth restriction (with small placentas). Hence, we believe that cardio-aspirin will not prevent the development of FGR in pregnant cancer patients. Proof for this hypothesis is found in placental studies. Only a limited number of (mainly animal) studies have been focusing on placental changes due to maternal cancer (treatment).[74] Maternal cytotoxic treatment penetrates the placenta and subsequently might affect placental development and fetal growth. Deficient placental nutrient and oxygen supply account for up to 90% of all SGA pregnancies in the general population.[103,362] The placental weight of untreated tumor-bearing animals is significantly reduced in comparison with non-tumor bearing controls and morphologic differences have been observed.[347,348] Also an increased level of oxidative stress and an affected DNA repair system in placental tissue have been noticed.[348,363] To date, only two studies have been evaluating chemotherapy-related placental changes in women. The first showing non-specific placental findings including villous hypoplasia (n=13) and the second confirming enhanced oxidative damage (n=25).[349,364] Genetic changes have been only studied after exposure to alkylating agents in non-tumor bearing animal models, confirming dose-dependent DNA-adduct levels in placental tissue and methylation of placental DNA, endorsing the oncogenic character of these drugs.[365,366] Placental irradiation effects have only been studied in one mice study, showing no morphological changes, but reduced placenta weights and significantly altered expression of genes related to oxidative damage.[367] Clinical studies also revealed small placentas in women with cancer, mainly in women who received chemotherapy.[74,98,349]

In multivariable analysis, we revealed that neonatal birthweight is negatively related to an earlier gestational age at diagnosis and a longer duration of chemotherapy during pregnancy (chapter 1 and 6). Our analyses suggest there is a dose-response effect between the amount of chemotherapy given in pregnancy and the eventual neonatal birthweight (chapter 1). It is important to highlight that multiple factors contribute to

impaired fetal growth in pregnant cancer patients: the aggressiveness of the cancer, cancer-related inflammation and the impact on general health status of the women, the psychological stress of a cancer diagnosis, the co-medication given (often steroids that are known to impact fetal growth), (age-related) hypertension, maternal age, smoking,… Women with cancer are a high risk population, whether or not cancer treatment is initiated during pregnancy. While the fetal genotype that determines the growth potential won't be affected, cancer is able to attack the developing fetus directly (by cancer treatment) and indirectly (by maternal psychological stress, oxidative stress and inflammation) by interfering with the in utero environment.[43] Growing evidence suggests histopathological, cellular and genotoxic changes in the placentas of pregnant cancer patients that will undeniably affect the capacity of the placenta to provide nutrients to the fetus.[74] We show a strong association between chemotherapy duration and lower birthweight percentiles, however the duration of chemotherapy used in the analysis can serve also as a proxy of the duration of exposure to cancer-related maternal stress, general inflammation, oxidative stress,… . Whether it is a direct dose-response effect of chemotherapy on fetal growth, or an indirect effect by all other cancer-related mechanisms affecting fetal growth, can be debated. Most likely it will be a combination thereof. It is the first time in literature we demonstrated the negative impact of maternal weight gain on neonatal birthweight in women with cancer. A general healthy nutritional status is a crucial component for cancer patients in order to cope with physical illness.[368] Also, cancer-related mental health problems (depression, anxiety), a plausible contributing factor to the failure to thrive in cancer patients, are suggested to be independent risk factors for adverse obstetric outcomes (low neonatal birthweight, SGA and preterm delivery).[68,369] We recommend an encouragement and optimization of nutrition and mental health (by stress reduction) in this high risk population.

Maternal prognosis of women with cancer

Evidence in the literature that pregnancy itself does not necessarily impacts survival is rather solid.[8] Over the years we see that more women are treated with chemotherapy during pregnancy.[100] The use of chemotherapy during pregnancy does however raise two main issues. First of all, chemotherapy crosses the placenta and can impact fetal development and growth, and long-term health of the child. Here, available studies on pediatric outcome are reassuring on the short-term.[40,113] An important second concern are gestational physiological changes resulting in chemodilution and reduced drug efficacy .[126,127,129] In order to obtain comparable plasma concentrations as in non-pregnant women, it is suggested that a significant chemotherapeutic dose increase would be required to achieve comparable plasma concentrations.[126] Caution is warranted as most cytotoxic drugs have narrow therapeutic windows and steep dose-response curves. Because of the fear for maternal and fetal toxicity and the available evidence on a preserved maternal prognosis, currently chemotherapeutic drug dosages are not increased, however are prescribed based on the actual body weight of pregnant patients.[126]

Is chemotherapy in pregnancy efficient at the current doses that we are giving, despite the pharmacological changes in gestation?[126,128] It is an important research question, as we tend to treat cancer during pregnancy in order not to delay treatment and preserve pregnancies in women of whom future fertility options might become limited or even impossible. This PhD builds evidence that survival of pregnant women with Hodgkin lymphoma and breast cancer is comparable to non-pregnant controls, even in the subgroup that is treated with chemotherapy during pregnancy (chapter 7 and 8).

Research on survival in pregnant women is hampered by the rarity that cancer coincidences pregnancy. By international collaboration we were able to collect data on maternal outcome. A major concern in this retrospective, international research is the oncological staging techniques that were used to stage pregnant women and non-pregnant controls. Obviously, during pregnancy concerns on fetal radiation exposure limit imaging and treatment options, which might lead to inferior staging and response evaluation. Pregnant women in the university hospitals of Leuven are staged with whole body diffusion weighted MRI (without the use of gadolinium), a very sensitive technique that was validated for staging in pregnant breast cancer patients in their monocentric study.[370,371] However, this technique is not validated for staging in non-pregnant patients with Hodgkin lymphoma or breast cancer. For Hodgkin lymphoma is a PET (Positron Emission Tomography) scan still the golden standard, both at diagnosis as during treatment evaluation and follow-up.[140,371] Fetal concerns limit the use of this imaging technique during pregnancy, especially because whole body MRI appears to be more safe in all trimesters of pregnancy.[237] Also, not all hospitals have this technique and/or experts in this field of imaging available. Hence, pregnant women diagnosed in hospitals other than Leuven are potentially not properly staged at primary diagnosis and actually presented with a more advanced stage of cancer in pregnancy, compared to the stage that was registered in the INCIP database. Nevertheless, maternal survival of pregnant women, who are potentially improperly staged, appears to be comparable to non-pregnant women.

A second bias in the research of maternal outcome following chemotherapy in pregnancy is the lack of details on chemotherapy dosages used in the pregnant women with cancer. Currently chemotherapeutic drug dosages are not increased, however are prescribed based on the actual body weight of pregnant patients.[126] As survival in pregnant women is reassuring, this PhD thesis further strengthens these clinical recommendations. However, in our analysis we were only able to assume that chemotherapy in registered pregnant women was dosed according to current recommendations. We took the liberty of this assumption because registered women were treated at tertiary, mostly university hospitals that participated in the international INCIP project, most likely following the up-to-date guidelines. However, we were unable to verify the dose regimens in all available cases.

For Hodgkin patients, we collaborated with the University hospital of Groningen (Mar Bellido and Wouter J. Plattel), as well as University Medical Center of Rotterdam (Pieternella Lugtenburg) for data collection of non-

pregnant premenopausal women. The cohort confirms on a larger scale what was previously published in four other retrospective series: a maternal outcome following Hodgkin lymphoma equal to the non-pregnant population.[85,109,141,142] Hence, this study is unique as survival of women treated during pregnancy is assessed in a sub-analysis. Also, it is the greatest series that includes non-pregnant controls, matched by age, stage and year of diagnosis for survival analysis. The rarity of women with a diagnosis of HL during pregnancy, explains the wide interval of inclusion. Importantly, the treatment of Hodgkin lymphoma has remained constant since the 1970s and ABVD (combination of doxorubicin, bleomycin, vinblastine, dacarbazine) is still considered the standard chemotherapy, so data obtained many years ago are still relevant today.

For breast cancer patients we collaborated with the German Breast Group, a team of experts in the field of cancer research. We focused on the subgroup of women treated during pregnancy, as survival of pregnant breast cancer patients in general was already investigated in a previous collaboration with the German Breast Group (GBG).[138] We collected a large cohort of 662 pregnant patients and 2081 non-pregnant breast cancer patients, carefully selected based on complete data. We used 'recent' cases, diagnosed after 2000, in order to create a cohort of women treated for breast cancer as uniform as possible, according to the most recent guidelines.[4,361] This was a large group of pregnant women, however we should acknowledge that this cohort was still not large enough to further pinpoint survival of specific subgroups, such as women treated with neo-adjuvant chemotherapy and women diagnosed with hormone-sensitive breast cancer during pregnancy. Survival of these women at risk needs further attention in future research.

A recent population-based retrospective study comparing overall mortality of 156 pregnant breast cancer patients with 11 110 non-pregnant women with breast cancer, showed an excess mortality in pregnant women the first 2 years after cancer diagnosis [Hazard ratio 2.28 95% Confidence Interval (1.48-3.52), when adjusting for age and period of cancer diagnosis; HR 1.62 95%CI(1.05-2.50) when adjusting for age, period of cancer diagnosis, positive lymph nodes (0, 1-3, ≥4), tumor size (0-20 mm, 21-50 mm, > 50 mm), estrogen receptor (ER) status (negative, positive), and malignancy grade (I, II, III, not graded)].[372] Long-term survival, however, was comparable between pregnant and non-pregnant women. The control group consisted of women with breast cancer who were non–pregnant at diagnosis and either had breast cancer 5 or more years after the latest pregnancy or had never been pregnant at diagnosis. The cohort was restricted to women registered in the Danish Cancer Registry with a primary breast cancer diagnosis at ages 15-44 years during 1973-2016. There was no information on antenatal management in the pregnant group. The larger cohorts of GBG/INCIP did not focus on short-term survival, however had the same reassuring conclusions on the long-term survival.[138,161] It is important to acknowledge some limitations of the analysis focusing on short-term survival. Compared to the GBG/INCIP research the authors included stage 4 breast cancer patients for analysis. Staging imaging techniques during pregnancy were not further specified. Potentially pregnant women were not properly staged during pregnancy due to fetal concerns, with stage 4 cancers missed at initial diagnosis, however picked

up after delivery when more detailed staging was performed. Importantly, the authors assessed overall mortality in the first 2 years from cancer diagnosis, potential including cases of maternal death following obstetric causes. During the long study period, substantial changes in treatment have occurred for breast cancer in general as well as for breast cancer during pregnancy. A potential negative effect on survival of treatment delay due to pregnancy in more ancient cases cannot be ruled out.

Another important remark on the research of maternal outcome following cancer diagnosis during pregnancy is the so feared delayed diagnosis in pregnancy. Pregnancy symptoms might mimic cancer symptoms, causing pregnant women to attribute physical discomfort to pregnancy and not to seek medical advice immediately. Especially in breast cancer, it is stated that pregnant women often present with more advanced stage in pregnancy with adverse tumor characteristics including lack of estrogen receptors and high malignancy grade.[4,131,138] However, this might evoke a 'chicken or the egg' causality dilemma. Is it the delayed diagnosis that explains the higher cancer stages seen in pregnant women, or is it the pregnancy itself that accelerates cancer growth? For the latter, when focusing on the largest cohorts on breast cancer in pregnancy that adjust for tumor characteristics, there are no clinical data that suggest this.[131,137,138] However, recent clinical studies showed that breast cancer diagnosis in late pregnancy had more aggressive or advanced tumor characteristics compared to a diagnosis in early pregnancy.[373,374] It is suggested that a heterogeneous group of breast cancer patients should be redefined based on trimester of diagnosis. Also, postpartum breast cancer is suggested to be a distinct entity with aggressive clinicopathological features compared to breast cancer diagnosed outside of pregnancy.[130,354] This might be the cornerstone for further research into the carcinogenesis of breast cancer in pregnancy and lactation.

Future perspectives

Cancer diagnosis in young pregnant women challenges oncological decision-making. The international network on cancer, infertility and pregnancy (INCIP) aims to build on clinical recommendations based on worldwide collaborative research. Results of reports on obstetric and neonatal outcomes of pregnant women with cancer resulted in practical recommendations for clinicians.[3,5] Currently, INCIP analyses and publications are very complete and evidence on most common cancer types is already very solid, answering most clinical research questions. However, in the fast evolving field of oncology there are many novel treatment strategies that need evaluation in pregnant patients. Most knowledge of new therapies comes from women who accidentally become pregnant during pregnancy and these rare data need to be collected in order to guide physicians in their counselling. This is an important reason that the INCIP database should continue to exist. Adding the heterogenic character of the population with all the different types of cancer occurring at different gestational ages, an experienced multidisciplinary team is indispensable in order to provide optimal care for both mother and child.

Clinical research on maternal prognosis following cancer in pregnancy is challenging because of the rarity of cancer in pregnancy. It takes a long time to collect sufficient data and international collaboration is mandatory. The research on maternal prognosis following breast cancer still has a lot in store. The effect of gestational age, as suggested in literature, was out of the scope of this PhD project.[373] Postpartum breast cancer, especially when diagnosed following breastfeeding, is suggested to be a distinct entity with more aggressive tumor characteristics.[130,354] Pregnant women diagnosed in late pregnancy may also have pregnancy-induced changes in the tumors. Also, clinical research should further focus on the tumor response in pregnant women treated with neo-adjuvant chemotherapy. Molecular research, to investigate the carcinogenesis of breast cancer in pregnancy and the behavior of ER-negative and ER-positive breast cancer cells, might have the potential to explain the inconsistent results in maternal survival following breast cancer in pregnancy in the available literature.

Management of pregnant cancer patients is challenging and for this reason a Belgian and an international Advisory Board on Cancer Infertility and Pregnancy (ABCIP) was born (www.ab-cip.org).[162] The INCIP database is the cornerstone for future patient-specific as well as general recommendations for management. Although analyses of the dataset are finite, the ABCIP will live a long life and is the fulfillment of all the knowledge and expertise that was built over the years by a continuously growing network of specialists with a special interest in pregnant women with cancer. This PhD reveals that pregnant cancer patients carry multiple risk factors for impaired obstetric outcomes. Nevertheless, this highlights even more the necessity to manage these women in experiences centers with high-risk obstetric units. ABCIP can give recommendations for management based on evidence-based and up-to-date information, but in the end a pregnant patient should be guided by an experienced multidisciplinary team with an holistic approach to cancer in pregnancy, including oncological, obstetric, psychological and nutritional risks. Undeniably, obstetric management should not be guided only by the pursuit to achieve full term delivery and should rather be based on an ad hoc risk assessment in case maternal or fetal deterioration occurs.

Conclusion

Chemotherapy in pregnancy for breast cancer and Hodgkin lymphoma does not seem to impact maternal survival. The undoubtedly progress we made in preserving the pregnancy when at the same time cancer is diagnosed, is associated with an increased risk of obstetric complications (spontaneous preterm delivery, negative impact on intra-uterine fetal growth). Knowledge of risk factors including the use and timing of chemotherapy, cancer stage and maternal nutritional status is crucial to tailor and organize the obstetric follow up. Indeed, care for pregnant cancer patients continuously requires balancing of maternal and fetal benefits and risks.

Scientific acknowledgement, personal contribution, and conflict of interest

Scientific acknowledgements and personal contribution

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Part I: INCIP registration study

The study designs, interpretation of the data and writing the manuscripts was done by myself with the assistance of Frédéric Amant, Kristel Van Calsteren, Mathilde van Gerwen (chapter 3, part follow-up of children) and Joosje Heimovaara (chapter 1). I would like to thank the medical staff of the University hospitals of Leuven for their clinical support and advice in the manuscripts of renal and bladder cancer (Maarten Albersen), Hodgkin and non-hodgkin lymphoma (Daan Dierickx, Peter Vandenberghe, Sherida Woei-A-Jin and Thomas Tousseyn) and breast cancer (Patrick Neven). I am responsible for all statistical analyses, the statistical interpretation and writing of the manuscripts. I received statistical advice and help of Annouschka Laenen

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Authorship of all publications in this PhD was defined by numbers of cases included, according to INCIP regulations (specified at www.cancerinpregnancy.org). All authors were involved in manuscript revision and approved the final version of the manuscripts.

Part II: Impact of chemotherapy during pregnancy on fetal growth

We thank all patients who consented to have their data registered and all (para-)medical staff who was involved in registering cases in the INCIP database. In particular, I would like to thank Kristel Van Calsteren, who guided and supervised me in the clinical practice of prenatal ultrasound in the University Hospitals of Leuven. Indeed, the majority of pregnant cancer patients who attended the hospital from August 2017 until July 2020 were scanned by myself with the supervision of Kristel Van Calsteren. Also, I am grateful to Paul Berveiller, Johannes Duvekot, Rebecca Painter, Ingrid Boere, Bianca Masturzo and Evgeniya Polushkina to provide prenatal scan information for this project. The study design, interpretation of the data and writing the manuscripts was done by myself with the assistance of Frédéric Amant, Vera Wolters (Study design and collection of Dutch data) and Kristel Van Calsteren. I am responsible for the statistical analysis, with the help of Annouschka Laenen, Vera Wolters and Joosje Heimovaara. All authors were involved in manuscript revision and approved the final version of the manuscripts.

Part III: Maternal oncological prognosis

For the breast cancer project, we thank all patients that consented to have their data registered and all parties involved in registering cases in the INCIP and GBG database, such as the medical specialists, data managers, secretaries and outpatient clinic departments of participating centers. I would like to thank the medical staff involved in the Breast Cancer Database of the University Hospitals of Leuven, especially Chantal Remmerie, to provide me with the data for non-pregnant breast cancer controls. In particular, I would like to thank Sibylle Loibl, Sabine Seiler, Valentina Nekljudova and Fenja Seither for their scientific collaboration and the multiple meetings that enabled this project. The study design, interpretation of the data and writing the manuscripts was done by myself with the assistance of Frédéric Amant, Sibylle Loibl, Sabine Seiler, Valentina Nekljudova and Fenja Seither. I was responsible for the collection of INCIP (follow-up) data and statistical interpretation. Statistics were performed by Valentina Nekljudova. All authors were involved in manuscript revision and approved the final version of the manuscripts.

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Conflict of interest statement

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- IELTS certificate 2016
- GCP certificate 2015

List of publications

Journal articles related to this thesis manuscript

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- Maggen C, Van Calsteren K, Wolters V, Verheecke M, Mhallem Gziri M, Amant F. Chemotherapy during pregnancy appears to impact fetal growth velocity. *Poster abstract:* World Congress Fetal Medicine Foundation, June 2018, Athens, Greece.
- Maggen C. Maternal breast cancer diagnosed during pregnancy. *Oral presentation:* ISOM Congress, October 2018, Amsterdam, The Netherlands.
- Maggen C, Management of women with breast cancer during pregnancy. *Oral presentation:* DEXEUS forum, January 2018, Barcelona, Spain.
- Maggen C, Van Calsteren K, Cardonick E, Shmakov R, Mhallem Gziri M, Cabrera Garcia A, Fruscio R, Lok, C, Halaska M, Boere I, Zola P, Ottevanger P, de Groot C, Scarfone G, FumagalliM, Painter R, de Haan J, Amant F. Obstetric outcome and maternal survival of Hodgkin lymphoma patients diagnosed during pregnancy: results from the INCIP registry. *Poster presentation:* ESMO 2019, September 2019, Barcelona, Spain.
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