Child development after maternal cancer diagnosis and treatment during pregnancy

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Child development after maternal cancer diagnosis and treatment during pregnancy

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CONTENTS

Chapter 1.

General introduction and outline thesis

A 32-year-old woman became pregnant. At 12 weeks of gestation the non-invasive prenatal test (NIPT) was performed. The test revealed an aberrant result. Analysis showed that the discordant results were maternal in origin; obstetric ultrasound showed a viable, intra-uterine pregnancy. The presence of tumor-derived cell-free DNA skewed the NIPT profile and was the result of a maternal malignancy. A computed tomography scan, without the use of contrast, and a biopsy confirmed the diagnosis of Non-Hodgkin lymphoma at 20 weeks of gestation. Receiving the diagnosis was stressful and overwhelming for the patient and her partner. It was their first pregnancy and, at the time of diagnosis, the pregnancy had already reached the halfway point. The physicians informed her that initiating immediate chemotherapy was imperative for a favorable prognosis. Additionally, the possible risks for her unborn child were carefully considered, as cancer treatment may have an impact upon fetal development. It is well known that chemotherapy interferes with cellular mechanisms and therefore may affect fetal cell growth. All possible treatment options were discussed by the National Advisory Board on Cancer in Pregnancy. Since previous studies showed that chemotherapy during the second and third trimester is relatively safe for the fetus, and starting treatment was imperative for maternal survival, the National Advisory Board on Cancer in Pregnancy and attending physicians advised her to start treatment. In consultation with her partner, the patient decided to follow the advice and she received five cycles of R-CHOP during pregnancy. The rosy glow of their first pregnancy had become clouded by the fear for the life of mother and the baby…

CANCER IN PREGNANCY

The incidence of maternal cancer during pregnancy is estimated to be one in 1000 to 2000 pregnancies.[1-3] This rare combination is expected to become more common as women in developed countries postpone their pregnancies until a later age, with the rate of most cancers increasing with age, and because of improved diagnostic procedures and detection of cancer. As of April 2017, all pregnant women in the Netherlands can choose for a non-invasive prenatal test (NIPT). The NIPT can be performed at 10 weeks of pregnancy and examines the DNA in the blood of the mother for chromosomal abnormalities in the child. An abnormal NIPT result can also indicate the presence of a maternal malignancy. While this highlights the possibility for early detection of cancer in pregnant women, a pregnancy can also challenge the diagnosis of cancer, thus leading instead to a delayed diagnosis. Cancer-related symptoms can be masked by symptoms of pregnancy such as fatigue, nausea and abdominal pain. Furthermore, in breast cancer patients, physiological changes of the breast during pregnancy might delay diagnosis: it is estimated that pregnant patients are at a 2.5-fold higher risk of being diagnosed with locally advanced breast cancer compared to non-pregnant patients.[4] In addition, when deciding on diagnostic imaging in pregnancy, some imaging tests are not recommended or even contra-indicated during pregnancy.

In 2005, the International Network on Cancer, Infertility and Pregnancy (INCIP) created a registry of women diagnosed with cancer during pregnancy. A current update of the registry is shown in Figure 1 with a data cutoff at April 2021. The most common diagnosed cancers during pregnancy are breast cancer (41%), lymphoma (12%), cervical cancer (11%), leukemia (8%) and ovarian cancer (6%). The types of cancer in the non-pregnant population are similarly distributed as in the pregnant population and are geographically defined. Older maternal age, high socio-economic status, multiparity, multiple pregnancy and prior diagnosis of cancer are retained as risk factors for an oncological diagnosis during pregnancy.[2,3,5]

A cancer diagnosis during pregnancy imposes a medical-ethical dilemma due to potential risks for the fetus. The current view is that the treatment stays as close as possible to standard treatment. For many cancer types surgery, radiotherapy and/or chemotherapy are the keys of oncologic treatment. Surgery can be performed safely in pregnancy as long as certain anesthetic and surgical precautions are made. Radiotherapy is often postponed until after delivery. However, if an adequate distance between the fetus and the field of radiation can be guaranteed, as in head and neck cancers, radiotherapy can be considered. In clinical practice, the fetal exposure should be below the threshold dose of 100mGy.[6] The timing of chemotherapy is a contributing and crucial factor to fetal outcome. Chemotherapy during the first trimester is contra-indicated as it is associated with spontaneous miscarriage, fetal death and congenital malformations.[7] From the second trimester onwards, chemotherapy

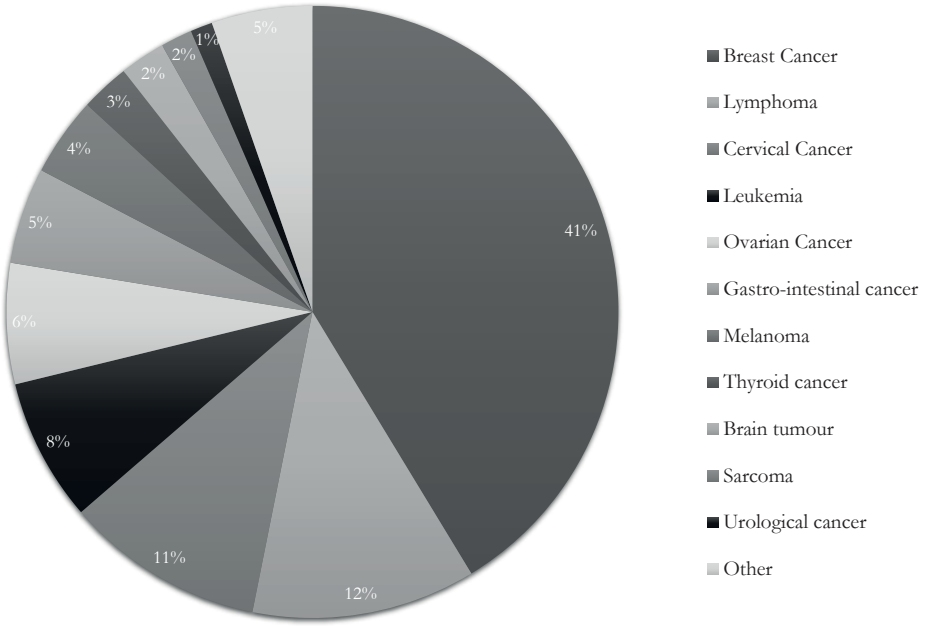

Figure 1: Distribution of cancer types diagnosed during pregnancy (N=2400, April 2021)

is considered as relatively safe, since the placenta may act as a protective barrier by reducing the fetal exposure to chemotherapy. Animal studies and ex vivo human studies on the transfer levels of chemotherapeutic drugs found that their materno-fetal passage is variable. The most frequently used chemotherapeutics in pregnancy had relatively low fetal transfer rates but varied from 1.4 to 57%.[8,9] The favorable fetal safety data from the pilot studies suggest that the placenta shields a proportion from the fetus. Nevertheless, the exact transplacental passage mechanism remains unknown because clinical studies are impossible to conduct and varying drug concentrations and combinations in the treatment of cancer patients challenge the research. Therefore follow-up of the offspring and robust evidence on the long-term consequences of antenatal exposure to chemotherapy is needed.

The treatment of pregnant women always requires a delicate balance in the consideration between maternal benefits and potential fetal risks. In the past this led to substantial termination of pregnancies in order to save the life of the mother. However, over the years clinical studies have showed that antenatal cancer treatment is possible and safe.[10-12] These studies led to a decrease in pregnancy terminations and strengthened the theory that oncological treatment in pregnancy is feasible under well-defined circumstances. In these high-risk pregnancies, surveillance by a multidisciplinary team in a specialized center and regular evaluation of maternal and fetal well-being is highly recommended, always taking the patient and her family perspective into account.[13]

SHORT TERM RESULTS

The neonatal outcomes of children exposed to chemotherapy are well studied. When chemotherapy is administered from the second trimester onwards, the risk of birth defects seems reassuring. In a review of 25 articles, each describing at least 50 patients, the incidence of congenital malformations after chemotherapy exposure during the second and/or third trimester is no higher than in the general population.[13]

The most commonly reported neonatal outcome is the high incidence of iatrogenic preterm delivery in pregnancies complicated by cancer. Preterm delivery may be induced by therapy planning or maternal deterioration. In a study by Amant et al. (2015), preterm birth was common (61.2%) and associated with a worse cognitive outcome. This effect was independent of cancer treatment. The conclusion resulted in a change in the management of pregnant women with the intention to deliver after 37 weeks of gestation.[13] Currently, the overall frequency of premature birth in patients with cancer during pregnancy is 48%, in contrast to a frequency of 6-8% in the normal population.[14,15]

Small for gestational age (i.e. a birth weight below the tenth percentile of gender- and gestational age-matched children) is another complication that is commonly reported when chemotherapy is administered during pregnancy. Cohort studies show inconsistent findings about the risks factors of small for gestational age (SGA). In the largest study up to date, 21% of the fetuses were born SGA. In this study, platinum-based chemotherapy during pregnancy was defined as a risk factor.[13]

In general, children exposed to chemotherapy seem to be at an increased risk for NICU admission due to complications that can occur in a pregnancy complicated by cancer. The main indication for NICU admission was related to prematurity and dependent upon malignancy type (with gastro-intestinal cancers having highest risk and thyroid cancer the lowest) and chemotherapy (with taxanes having the highest risk).[13]

As the development of the central nervous system starts begins during pregnancy and continues after birth, the long-term consequences of the maternal malignancy and antenatal cancer treatment are important to consider and still a serious concern.
How do these children develop in the long-term?

FOLLOW-UP OF CHILDREN

Data on the long-term impact of children exposed to maternal malignancy and its treatment on general health, cognitive, cardiologic, behavioral and neurological development are scarce. To address the short and long term effects, children exposed to antenatal cancer and cancer treatment are followed in an international multicenter follow-up study by

INCIP. This study started on March 2005 at University Hospitals Leuven Belgium and currently five other European Centers are collectively involved using a harmonized follow-up protocol. Since June 2018 the follow-up for Dutch children was nationally centralized in the Princess Máxima Center for pediatric oncology in Utrecht. In this center an outpatient expertise clinic for children born from pregnant woman with cancer, named 'Cancer In Pregnancy outpatient clinic' was established. The centralization of the follow-up of the Dutch cohort was an important turning point of the data collection, since then almost 150 Dutch children who are prenatally exposed to maternal cancers and its treatment have been enrolled. Children are prospectively examined through a general neurologic and physical examination, neuropsychological examination and an electrocardiogram (ECG) and echocardiographic assessment at regular time points (at birth, 18 months, 3 years and then every three years until the age of 18). This thesis mainly focused on the (neuropsychological) outcomes raised from this follow-up study.

PEDIATRIC OUTCOMES

In 2012, the first interim analysis of this multicenter cohort study was performed. In total 70 children with a median follow-up period of 22.3 months were included. In general, children prenatally exposed to chemotherapy showed a normal neurodevelopment; however, 29% of these children had increased scores for internalizing, externalizing or total problems as compared to the general population. Furthermore, prematurity was associated with a worse cognitive outcome and nine children (13%) had a disharmonic intelligence profile. Electrocardiographic results revealed no arrhythmia or conduction abnormalities, although a higher heart rate was observed in children exposed to chemotherapy. During echocardiographic examination, the ejection fraction, fractional shortening and interventricular septum thickness were slightly decreased in study versus control children. Some of the heart-rate dependent diastolic variables were significantly different between the patient and control group. Mitral valve E velocity was lower, mitral valve A velocity was shorter and isovolumetric relaxation time was shorter in the study group. Nevertheless, all measurements were still within the normal range.[12]

In 2015, the outcome of 129 children (mean age, 22 months; range 12 to 42 months) whose mothers had a diagnosis of cancer during pregnancy was compared with 129 children born after an uncomplicated pregnancy and delivery. Children were matched with respect to gestational age at birth and age at testing. The cognitive, cardiac and general development of children who were exposed to chemotherapy did not differ between both groups. The authors concluded that chemotherapy had no clear, adverse, short-term effect on postnatal growth or on cognitive or cardiac function. In addition, this study found that

preterm birth was an independent predictor of poorer cognitive outcome and this effect was independent of the cancer treatment.[16]

In general, these results are reassuring, since maternal malignancy and its treatment had no clear adverse effect on postnatal growth or on cognitive and cardiac function. However, small numbers of children were used and the follow-up period was restricted to early childhood and therefore may be too short to document long-term cardiotoxicity and neurotoxicity. In addition, the results could not be extrapolated to all chemotherapeutic drugs and heterogeneity in the study group may mask significant differences.

The current thesis will build on these outcomes to shed light on the questions raised from these studies. As the central nervous system continues to develop after the first trimester and throughout pregnancy, chemotherapy administered during the second or third trimester of pregnancy may affect neurocognitive development. Cognitive problems may become more apparent with increasing age as tasks become more complex and challenging for the child's cognitive abilities. In addition, exposure to chemotherapy in children and adults with cancer can cause cognitive dysfunction. An array of long-lasting disturbances in cognitive functioning as attention, memory and executive functions has been described as 'chemobrain'.[17-19] Therefore, long-term follow-up studies that include a detailed neuropsychological assessment of cognitive functions at different ages are needed. Also, subtle differences in cardiac measurements in previous studies and the knowledge that cancer survivors are at risk for cardiotoxicity even decades after treatment highlights the need for an increase of the cohort sample and longer follow-up.

OBJECTIVES AND OUTLINE OF THE THESIS

The general objective of the research presented is to address the effects of prenatal exposure to maternal malignancy and its treatment, with a major focus on the neurocognitive development. In **Chapter 2** an overview of the current evidence and the management of cancer during pregnancy is provided. **Chapter 3** describes the congenital malformation rate according to gestational age at antenatal chemotherapy exposure. **Chapter 4** and **Chapter 5** address the long-term effects of maternal malignancy and its treatment on pediatric outcome. First, child development at 6 years of follow-up is evaluated and secondly two sub-analysis are performed on smaller cohorts to evaluate executive functions in children prenatally exposed to chemotherapy, and to evaluate neurocognitive development in children after a hematological malignancy in pregnancy. **Chapter 6** and **Chapter 7** try to disentangle the impact of various maternal malignancies and co-medications on short and long term fetal safety. In these chapters the single impact of gastric cancer and the effect of the supportive drug G-CSF is described. In **Chapter 8,** international guidelines based on a consensus meeting for children exposed to gynecologic cancers in pregnancy

are described. A general discussion, conclusion and summary are described in **Chapters 9** and **10**.

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Chapter 2.

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

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**These authors contributed equally*

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ABSTRACT

The diagnosis of cancer during pregnancy imposes a medical-ethical dilemma in weighing the risks of both mother and child. With the increasing awareness of the feasibility of cancer treatment during pregnancy, more pregnant patients receive cancer treatment. As a result, information on obstetric and pediatric outcome in these high risk pregnancies is highly needed to guide physicians in patient counselling. In this review we present reported evidence regarding the incidence, diagnostic options, therapeutic management, obstetric risks and neonatal outcome when cancer treatment is initiated during pregnancy. Decision-making when a cancer is diagnosed in a pregnant patient should be multidisciplinary, always taking the patient's perspective into account. Chemotherapy in first trimester should be avoided because of the impact on organogenesis and risk of congenital malformations. Cancer treatment during pregnancy is associated with low birth weight and preterm delivery, therefore frequent obstetric follow-up during oncological treatment in a specialized center is mandatory. Short term clinical, cardiac and cognitive outcome of children prenatally exposed to cancer treatment is overall reassuring. Long-term follow-up of children is warranted to define the possible effect of prenatal cancer treatment on general health, fertility outcome and the risk of secondary cancers.

INTRODUCTION

A cancer diagnosis during pregnancy imposes a medical-ethical dilemma as immediate aggressive treatment is often indispensable for maternal survival, whereas cytotoxic medication threatens fetal wellbeing by crossing the placenta.[1,2] Due to their mechanisms of action, all chemotherapeutic agents are potentially toxic to the fetus and thus maternal advantage must be always weighed against the possible risks for the unborn child.

When a pregnant patient is confronted with cancer, all treatment options should be discussed. In the past, termination of pregnancy was often the preferred advice because of the fear for toxic effects of drugs that are designed to eliminate rapidly dividing cells on the fetus. Abortion still remains the preferred option if fast initiation of aggressive systemic treatment that is not compatible with continuation of pregnancy (for example in case of first trimester diagnosis of acute leukemia) is indicated. However, in most cases, termination of pregnancy does not improve prognosis and for socio-economic religious reasons may not be an option in the perspective of the patient.[3] Also, the pregnancy may be the last chance of childbearing, as oncological treatment may affect fertility.

Increasing awareness of the feasibility of cancer treatment during pregnancy, resulted in a change in management with more pregnant patients receiving cytotoxic drugs for cancer.[4] Although administration of chemotherapy after the first trimester is considered to be relatively safe, it is of vital importance to ensure fetal wellbeing. Some of these agents have potential neuro- and cardiotoxic effects on the fetus. Use of chemotherapy after the first trimester may be associated with intra-uterine growth retardation, still birth, (iatrogenic) premature delivery, low birth weight and neonatal myelosuppression and sepsis.[5,6] 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.

In this review we give an overview of the current knowledge on the management and the obstetric, neonatal and pediatric risks of cancer treatment during pregnancy.

METHODS

First, we give an update on the current knowledge on the epidemiology, diagnosis and management of cancer during pregnancy. In order to summarize the reported obstetric and neonatal risks of oncological diagnosis and treatment during pregnancy, we searched PubMed on July 20th 2018, for articles on cohorts of patients with cancer during pregnancy that described obstetric, neonatal and pediatric outcomes, using the following keywords: “pregnancy”, “cancer”, “tumor”, “neoplasm”, “outcome”, and “neonatal outcome”. The search was restricted to publications in English, cohorts of at least 50 cases and publications between Jan 1, 1992, and June 31, 2018. References from the selected articles were

scanned in order to identify other papers. For the search of long-term outcome of children prenatally exposed to cancer or cancer treatment there was no restriction regarding year of publication or number of included cases. In total, 25 large cohort studies and 10 population based studies that reported on obstetric and/or neonatal outcome after a cancer diagnosis during pregnancy were selected. Pediatric outcome was reported in 10 cohort studies.

Epidemiology of cancer during pregnancy

Pregnancies complicated with a cancer diagnosis are poorly studied epidemiologically as national registries usually do not combine information on both cancer diagnosis and obstetrics. Nationwide linkage studies estimated the incidence of pregnancy-associated cancer, defined as a cancer diagnosis during pregnancy or within 12 months from delivery, to be one in 1000 to 2000 pregnancies.[7-9] As women in developed countries tend to delay childbearing, this rare combination is expected to become more common, as already demonstrated by population-based cohort studies. The incidence rate of pregnancy-associated cancer in Australia increased from 112.3 to 191.5 per 100000 maternities.[8] In this continent, the incidence of pregnancy-associated melanoma rose from 37.1 per 100000 maternities in 1994 to 51.84 per 100000 maternities in 2008.[10] A Canadian study found an increasing incidence of pregnancy-associated non-hodgkin lymphoma from 4.44 per 100000 births to 7.17 per 100000 births over the 9-year study period.[11] Improved diagnostic procedures, detection and more specialized interaction between health services during pregnancy might also contribute to the higher incidence rates. Between 2003 and 2011 ovarian masses were increasingly detected in Canadian patients, most likely due to the recommendation of routine prenatal ultrasound, whereas malignant masses remained relatively stable throughout the study period.[12]

In 2005 the International Network on Cancer, Infertility and Pregnancy (INCIP) started a registry of cancer in pregnancy. The first update on the obstetric and neonatal outcome of 215 patients was published in 2010.[13] An interim-analysis on 1170 patients, the largest cohort study published to date, was performed in 2017.[4] The research network continues to recruit patients with a cancer diagnosis in association with pregnancy and a current update of the registry is shown in figure 1. The most common cancers diagnosed during pregnancy were breast cancer (35%), lymphoma (13%), cervical cancer (11%), leukemia (9%) and ovarian cancer (8%). This distribution of various cancer type diagnoses in association with pregnancy is similar as seen in the non-pregnant population and is geographically defined.[8] Older maternal age, high socio-economic status, multi-parity, multiple pregnancy and prior diagnosis of cancer are retained as risks factors for an oncological diagnosis during pregnancy.[8,9,14]

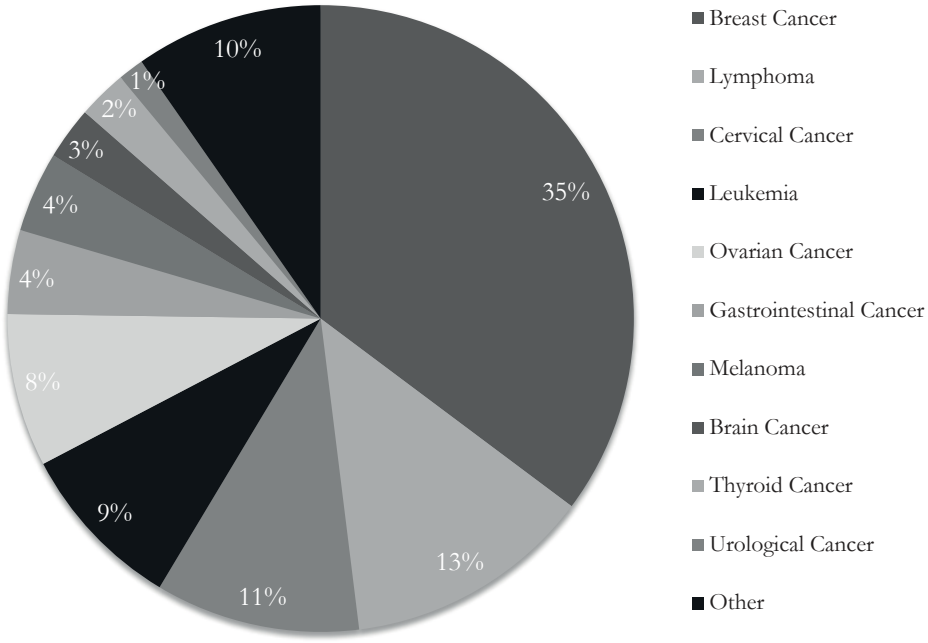

Figure 1: Distribution of cancer types diagnosed during pregnancy (N= 1732, August 2018). Data retrieved from the cancer in pregnancy study (August, 2018) by the International Network on Cancer, Infertility and Pregnancy

Diagnosis of cancer during pregnancy

Pregnancy induced physiological changes may challenge the diagnosis of several cancers, often resulting in a delayed diagnosis. It is estimated that a pregnant patient is at 2.5-fold higher risk of being diagnosed with locally advanced breast cancer compared to a non-pregnant patient, as physiological changes of the breast during pregnancy that might delay diagnosis.[15] A systematic physical examination and a low threshold for further investigations is crucial for an early diagnosis. The most optimal imaging is required to decide on further treatment and follow-up of the patient. When deciding on radiographic imaging in pregnancy, one should consider that only the exams that will influence the management should be performed and caution is warranted since the (accumulated) fetal radiation exposure may not exceed 100 mGy.[16] Therefore, MRI and ultrasound are the preferred staging examinations during pregnancy. Diffusion weighted MRI whole body is validated for the staging of cancer during all trimesters of pregnancy.[17] Ultrasound can be performed safely during pregnancy. In breast cancer a mammography (restricted to one medio-lateral oblique record of both breast and with abdominal protection in the second half of pregnancy) is advised. The sentinel-node procedure is considered to be safe enough during pregnancy, as long as the injected dose of Technetium-99m labeled colloid is as low as possible, with and estimated average fetal radiation dose is 0.45 mGy. Therefore, a one-day protocol is preferred. Blue dye, which is sometimes injected prior to surgery to

facilitate the detection of the sentinel node is not advised as this can potentially cause an anaphylactic reaction. Contrast products have to be used with caution in imaging. MRI of the breasts during pregnancy is not the preferred method, as gadolinium is contra-indicated. Fetal gadolinium exposure is associated with rheumatologic, inflammatory, or infiltrative skin conditions, stillbirth and neonatal death.[18] Iodinated contrast may cause neonatal thyroid dysfunction. If it is used during pregnancy, the thyroid function of the neonate has to be controlled within one week after birth.

Treatment options during pregnancy

In the management of cancer during pregnancy the key principle is that the treatment stays as close as possible to standard treatment of non-pregnant patients. However, from fetal perspective some treatments are not advised or even contra-indicated during pregnancy. If a pregnant patient presents with a very aggressive or metastatic disease in early pregnancy, it should be questioned whether the pregnancy can be conserved safely. If a low-grade malignancy is detected, treatment postponement until after delivery may be considered. Preferably, decision-making should be performed in a specialized center by a multidisciplinary team, always taking the patient's perspective into account.

Surgery

An intervention can be performed safely during the pregnancy, as long as some anesthetic and surgical adjustments are made. A stable oxygenation and stable blood pressure are mandatory to maintain an optimal fetal condition. In pregnancy the use of oxygen is raised and the functional residual capacity of oxygen reduced, resulting in a fast desaturation when apnea occurs. Maternal hypotension as a result of deep anesthesia, hypovolemia and vena cava compression, may cause uterine hypoperfusion. Therefore, left lateral tilt position from 20 weeks gestational age onwards is advised. From a viable duration of pregnancy (usually 24 weeks of gestation, depending on local hospital policies and patient perspective) intraoperative fetal monitoring is advised whenever possible. Tocolytics are advised during the second and third trimester of pregnancy if uterine manipulation during surgery is inevitable.[19] A laparoscopic intervention during pregnancy can be performed until 26-28 weeks of gestation, depending on the surgeon's expertize.[20] An open introduction by Hasson is the preferred method. The umbilical port should be located 3-4 cm above the uterine fundus, even if this location is supra-umbilical. CO_2 insufflation of 10-15 mmHg can be safely used and maximal duration of the intervention is ideally 90 minutes. Postoperative analgesia is important as pain may provoke preterm uterine contractions. Non-steroidal anti-inflammatory drugs are contra-indicated in pregnancy because of the risk of preterm closure of the ductus arteriosus. In the postoperative setting, prevention of thromboembolism with low molecular weight heparin is indicated because of the hypercoagulable state of pregnancy and cancer.[21]

Chemotherapy

The ability of a drug to cross the placenta is defined by the physicochemical properties of 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. Studies on the transplacental passage of cytotoxic agents, including paclitaxel, carboplatin, doxorubicin and epirubicin demonstrated that the placenta acts as a barrier and the exposed fetal concentration is substantially lower than the maternal concentration.[1,2,22,23] Chemotherapy is contra-indicated in the first trimester because it can potentially disturb organogenesis and is associated with miscarriage, fetal death and congenital malformations.[24] Starting from the second trimester of pregnancy, the administration of cytotoxic drugs seems to be relatively safe. Since cytotoxic drugs are usually administered in a multi-drug regimen, it is difficult to estimate the effect of each drug. Ngu et al. recently reviewed available data on neonatal outcomes after the use of different chemotherapeutic agents during pregnancy.[25] The current evidence on placental passage and neonatal risks for several types of chemotherapy most commonly used during pregnancy is summarized in table 1. Physiological changes in pregnancy, such as the increased blood volume and increased renal clearance, lead to a decrease in peak plasma concentrations and active medication in plasma (area under the curve, AUC), as well as a raised distribution volume and elimination.[26] Theoretically this finding may suggest that a standard treatment dose of cytotoxic agents, which is based on the actual body weight may be suboptimal. To date no studies justify a change in dosage and the prognosis of patients treated for cancer during pregnancy does not seem to be different compared to non-pregnant patients.[27] However, more studies including larger numbers of patients with follow-up data and pharmacokinetic data are needed.

Table 1: 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**	**References**
Platinum compounds	Carboplatin, (Cisplatin)	± 60%	Risk of ototoxicity greater for cisplatin; use carboplatin in preference - **SGA** (OR 3.12 (1.45 – 6.70)) - NICU admission OR 1.66 (0.77 – 3.55)	Postnatal auditory test	[1], [4], [23]
Alkylating agents	Cyclophosphamide	± 20%	- SGA (OR 2.08 (0.88-4.91)) - NICU admission OR 0.88 (0.46 – 1.70)		[2], [4], [23]
Antimetabolites	5-Fluorocil	± 28%	- SGA (OR 1.24 (0.70 – 2.22) - NICU admission OR 1.03 (0.60 – 1.74)		[4], [22], [23]

Table 1: Current evidence on possible neonatal risks after prenatal exposure starting from the second trimester of pregnancy to most frequently used cytotoxic drugs (continued)

Drug class	Drug	Transplacental passage *	Neonatal risk (OR (95% CI))	Specific recommendation for neonatal follow-up	References
Antitumour antibiotics	Epirubicin	<10%	- SGA (OR 0.50 (0.21 – 1.22) - NICU admission OR 1.21 (0.62 – 2.38)	Postnatal fetal echocardiography	[2], [4], [23]
	Doxorubicin	<10% (active metabolite)	- SGA (OR 0.50 (0.21 – 1.22) - NICU admission OR 1.21 (0.62 – 2.38)	Postnatal fetal echocardiography	[2], [4], [23]
Taxanes	Paclitaxel, docetaxel	<2%,	Accumulation in neonatal tissue is feared as metabolisation by liver enzymes is not yet mature in the newborn - **SGA** (OR 2.07 (1.11 – 3.86) - **NICU admission** OR 2.37 (1.31 – 4.28)		[1], [4], [23]
Vinca Alkaloids	Vinblastin	± 20%	- **SGA** (OR 2.34 (1.04 – 5.25) - NICU admission OR 1.63 (0.78 – 3.38)		[2], [4], [23]

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

Targeted anti-cancer therapies and tamoxifen

Over the years, targeted therapy is more developed and is now used in the treatment of several types of cancers. Mostly the effect of these drugs during pregnancy is not known and use of targeted therapy in pregnant patients is discouraged because of the limited experience. 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 2 gives a brief overview of current evidence on neonatal risks when targeted therapy or tamoxifen is used during pregnancy.[28-32] A comprehensive review has recently been published.[33]

Table 2: 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	Reference
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	[28], [33]
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	[29], [31], [33]
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	[30], [33]
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	[31], [33]
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	[33]
Anti-angiogenetic agents: (1) bevacizumab, (2) sorafenib, (3) sunitinib	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	[33]
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	[33]

Table 2: Current evidence on possible neonatal risks after prenatal exposure to targeted therapy and tamoxifen (continued)

Drug	Function	Cancer type	Neonatal Risk	Recommendation for use during pregnancy	Reference
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	[32]

Radiation therapy

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. Fetal radiation exposure during radiation therapy is much higher compared to the exposure during diagnostic procedures. Pelvic irradiation, with direct effect on the fetus, should never intentionally be performed during pregnancy. For the upper body (f.ex. breast, brain) the total fetal exposure should always be calculated by a physicist using a phantom model. Radiation exposure during early first trimester can cause congenital malformations with a threshold dose of 0.1 – 0.2 Gy.[16] The central nervous system is sensitive to radiation during 8-25 weeks after conception and a dose of 0.1 Gy may result in a decreased intelligence quotient.[34] Radiation doses of 1 Gy are associated with up to 40% risk of several mental retardation.[35] In utero irradiation at all gestational ages may increase the risk of cancer during childhood.[36] In clinical practice, usually radiation after breast conserving therapy will be postponed until after delivery, to avoid the potential effects on the fetus.

Supportive therapy

Supportive medication in pregnant women should only be given if clinically indicated. During pregnancy anti-emetics like metoclopramide, cyclizine and meclozine can be safely used.[19] In case of insufficient effect, ondansetron (5HT antagonist), aprepitant (NK1 antagonist) and alizapride (dopamine antagonist) may be considered with care. Also, corticosteroids, growth factors (GCS-F) and erythropoetins are not adequately studied for their safety during pregnancy requiring surveillance of the fetus. These drugs are however mandatory for high dose schemes as used in some breast cancer patients. The use of hydrocortisone and prednisolone is preferred over dexa- or betamethasone as these are extensively metabolized in the placenta and relatively little will be detected in the fetal compartment. Repeated administrations of betamethasone are associated with attention problems and cerebral palsy.[37]

Obstetric management and delivery

Decisions about the best management in pregnancy, including timing of delivery, should balance maternal and fetal risks. In obstetric management a continuous evaluation of maternal and fetal wellbeing is primordial. Prior to chemotherapy exposure, fetal growth as well as fetal Doppler assessment and cervical length should be assessed. In this population, iatrogenic preterm delivery is not uncommon, as delivery will be mostly planned to optimize the timing of oncological treatment. However, prematurity is associated with neonatal mortality and morbidity on the short and long-term.[38,39] Therefore the tendency to avoid iatrogenic preterm delivery and start of treatment needs to be balanced against the neonatal risks. Ideally, delivery after 37 weeks of gestation should be intended. Delivery within 2-3 weeks following the last administration of cytotoxic drugs (depending on the regimen used) should be avoided to reduce the risk of myelosuppression and systemic infection. Therefore, a neonatal blood sample is recommended. A vaginal delivery should be aimed for, unless there is an obstetric or oncological contra-indication. Cervical cancer is an absolute indication for cesarean section in order to avoid fatal recurrences on the episiotomy scar. A corporeal incision may prevent abdominal wound recurrences. In gynecological cancers a cesarean section can be performed simultaneously with surgical treatment. Although rare, the placenta should be sent for histological examination to detect possible placental metastasis, mostly seen in malignant melanoma, followed by leukemia and lymphoma.[6]

OBSTETRIC, NEONATAL AND PEDIATRIC OUTCOME OF CANCER TREATMENT DURING PREGNANCY BASED ON PUBLISHED COHORT AND POPULATION-BASED STUDIES.

Obstetric outcome

The rarity of cancer during pregnancy and the variety of different cancer types has limited assessment of obstetric outcome and maternal events. Most information on obstetric risks for cancer patients comes from large population based cohort studies, summarized in table 3. However, several limitations of studies based on a linkage between cancer and birth registries should be acknowledged. Early pregnancy loss (miscarriage or termination of pregnancy) is not registered in birth data, leading to a slight underestimation of the incidence of pregnancy-associated cancer as well as an overestimation of the average gestational age at cancer diagnosis. Often these studies lack information on treatment modalities during pregnancy, preventing adjustment for cancer treatment in analyzes of adverse pregnancy outcomes. Obstetric outcome after breast cancer and hematologic malignancies during pregnancy is better studied than less common cancer types diagnosed during pregnancy.

Table 3: Reported obstetrical outcome and complications of cancer during pregnancy in the largest multicenter cohort study and population based cohort studies on 'Pregnancy-associated cancer'

Reported obstetrical outcome and complications								
Ref.	**No. patients**	**Years of inclusion**	**Countries**	**Type of cancer**	**Pregnancy outcome OR (95% CI)**	**Birth weight**	**Pre-eclampsia/HELLP PPROM and preterm contractions Systemic infection other**	**Neonatal outcome**
[9], Parazzini et al. 2017**	1475	2001-2012	Lombardy, Italy	All types	1025 Live birth (69.5%) 450 Abortion (30.5%) Increased risk for abortion OR 1·22 (1·09 – 1·37)	Not reported	Not reported	Not reported
[4], De Haan et al, 2018*	1170, 1089 singleton pregnancies with known obstetricout-come	1996-2016	INCIP #	All types	14 still birth (1%) 955 live birth (%) 95 termination (9%) 20 miscarriage (2%) 430 preterm birth (39%) 458 term birth (>37w (42%))	167/796 (21%) SGA	98 (10%) PPROM or preterm contractions 5 (<1%) Maternal death during pregnancy	4% Congenital malformations
[57], Lu et al, 2017**	948	1973-2012	Sweden	All types	Increased SGA related stillbirth (IRR 4·9, 95% CI 2·2 – 11·0) Increased preterm birth (OR 5·8 (5·3 – 6·5), mainly iatrogenic Increased CS rate (40% vs 12%)	Increased preterm SGA (RR 3·0, 95% CI 2·1 – 4·4), mainly hematological and ovarian cancers No increased term SGA (RR 1·0, 95% CI 0·7 – 1·3)	Not reported	Increased neo-natal mortality (IRR 2·7, 95% CI 1·3 – 5·6) (89% prematu-rity related)

Table 3: Reported obstetrical outcome and complications of cancer during pregnancy in the largest multicenter cohort study and population based cohort studies on 'Pregnancy-associated cancer' (continued)

Reported obstetrical outcome and complications								
[52], El Messidi et al, 2015**	638	2003-2001	Canada	Hodgkin Lymphoma	Increased risk preterm birth (aOR 1.93 (1.53-2.42)) No increased incidence still birth (1/638, 0.16%)	Increased risk VTE (aOR 7.93 (2.97-21.22) Increased risk blood transfusion (aOR 1.38 (1.05-1.82)	No increased incidence IUGR (15/638, 2.4%)	No increased incidence congenital malformations (5/638, 0.78%)
[10], BannisterTyrrell et al, 2015**	577 (195 during pregnancy, 382 postnatal diagnosis)	1994-2008	Australia	Melanoma	No increased risk of still birth (0/195), planned birth (OR 0.87 (0.61-1.23), CS (OR 0.98 0.70-1.38), prematurity (OR 0.82 (0.44-1.56)	Increased risk hypertension in pregnancy (OR 1.21 0.93-1.58))	No increased risk SGA 75% higher odds on LGA (OR 1.75 (1.22-2.53)	Not reported
[8], Lee et al, 2012**	499	1994-2008	Australia	All types	Increased risk of IOL (aOR 1·27, 95% CI 1·03 – 1·56) Increased risk of CS (aOR 2·08, 95% CI 1·70 – 2·54) Increased risk of iatrogenic prematurity (aOR 11·53, 95% CI 8·81 – 15·11), but no increased risk of spontaneous prematurity	Increased risk VTE (OR10.20(3.81-27.33)) Increased risk sepsis (OR 4.28 (2.57-7.13)) Increased risk severe maternal morbidity (OR 6.89 (4.66-10.19)) No increased risk obstetrical hemorrhage (OR1.10 (0.74-1.63))	No increased risk Increased risk LGA (aOR 1·47, 95% CI 1·14 81 – 1·89)	No increased risk of perinatal death

Table 3: Reported obstetrical outcome and complications of cancer during pregnancy in the largest multicenter cohort study and population based cohort studies on 'Pregnancy-associated cancer' (continued)

Reported obstetrical outcome and complications								
[11], El-Messidi et al, 2015**	427	2003-2011	Canada	Non-Hodgkin Lymphoma	Increased risk of CS (OR 1·37, 95% CI 1·13 – 1·67) Increased risk of prematurity (OR 2·50, 95% CI 1·94 – 3·22) No increased risk of IOL Increased risk of stillbirth (OR 2·71, 95% CI 1·12 – 6·55)	Postpartum blood transfusion (OR 2.73 (2.10-3.55)) Pre-eclampsia (1.57 (1.06-2.32)) Postpartum infections (OR 2.81 (1.16-6.79)) Maternal death (68.72 (21.94-215.27)) No increased risk VTE (OR 3.26 (- 23.13))	No increased risk (no IUGR in 427 cases)	No increased risk of congenital malformations (3/427)
[12], Nazer et al, 2015**	179	2003-2011	Canada	Ovarian Cancer	Increased risk of CS (OR 5·92, 95% CI 4·17-8·41) Increased risk of prematurity (OR 2·24, 95% CI 1·48 – 3·42) Maternal death (OR 6.78 .84-54.45) No increased risk of PPROM or stillbirth	Eclampsia OR 3.10 Placental abruption OR 1.15 Hysterectomy OR 60.90 VTE OR 5.52µ	No increased risk: IUGR (OR 0.20)	Not reported
[59], O'Meara et al., 2005**	145	1991-1999	USA	Melanoma	No increased risk: -Still Birth -Prematurity -CS	No increased risk compared to healthy controls	Not reported	No increased risks NICU admission or neonatal death

Table 3: Reported obstetrical outcome and complications of cancer during pregnancy in the largest multicenter cohort study and population based cohort studies on 'Pregnancy-associated cancer' (continued)

Reported obstetrical outcome and complications								
[58], Dalrymet al, 2005**	136	1991-1999	USA	Cervical cancer	Increased risk of CS (OR 3·7, 95% CI 2·6 – 5·2) Increased risk of prematurity (OR 4·7, 95% CI 3·2 – 6·7), both spontaneous and iatrogenic Increased risk of stillbirth (OR 5·5, 95% CI 2·0 – 14·8)	Increased risk of SGA (OR 5·5, 95% CI 3·7 – 8·1) Increased risk for extreme SGA (OR 6·9, 95% CI 3·7 – 12·8)	Increased risk maternal hospitalization (OR 14.1; 95% CI 9.2, 21.5)	Increased risk of neonatal admission (OR 5·2, 95% CI 3·6 – 7·5)
[14], Yasmeen et al., 2005**	129	1991-1999	USA	Thyroid cancer	No increased risk of prematurity or CS.	No increased risk (hypertension, antepartum hemorrhage, preterm delivery, CS)	Not reported	No increased risk of neonatal death

* International multicenter retrospective and prospective cohort study

** Population-based cohort study (by linkage of nationwide registries)

For countries in INCIP: see www.cancerinpregnancy.org

OR: odds ratio; aOR: adjusted Odd's ratio; IUGR: intra-uterine growth restriction; SGA: small for gestational age; CS: cesarean section; IOL: induction of labor; VTE: venous thromboembolism

The largest cohort 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.[4] 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 live birth among singleton pregnancies (RR 1·04, 95% CI 1·01–1·06), a reduction in the risk of preterm live birth (0·93, 0·86–0·99), and a reduction in the risk of iatrogenic preterm live birth (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 increased (1·16, 0·99–1·35).

The high incidence of iatrogenic preterm delivery in pregnancies complicated by cancer was already reported in previous series.[7,8,13] Maternal deterioration, optimal timing of cancer treatment or the need to start with therapy that is not compatible with pregnancy may force early delivery. Also, the administration of chemotherapy is associated with PPROM or spontaneous preterm contractions and labor.[11,13,40] Chemotherapy-induced weakening of the amnion-chorion membrane may be a possible explanation.[41] Stress of a cancer diagnosis may potentially activate the maternal hypothalamic-pituitary-adrenal axis, provoking labor by the release of oxytocine.[42] The cesarean section rate in patients with a cancer diagnosis during pregnancy appears to be higher compared to the normal population.[8] This is likely to reflect the standard management of certain types of cancer (f. ex cervical cancer), but may also be attributed to the comfort of a planned, controlled delivery.

Neonatal outcome

Clear evidence exists on the risk of birth defects when chemotherapy is administered during the first trimester, the crucial timing of organogenesis, which occurs roughly 2 to 8 weeks post-conception. In cohort studies where mothers initiated treatment in the second trimester of pregnancy, the incidence of congenital malformations was not increased.[43,44] The first large observational study that reported on fetal safety when cancer was diagnosed during pregnancy evaluated the neonatal outcome of 116 children, of whom 106 were

prenatally exposed to chemotherapy.[45] There was no difference in the congenital malformation rate (3.8%) of the chemotherapy exposed children compared to the general population. Larger and more recent studies confirmed this with no higher incidence of congenital malformations and equivalent rates compared to the general population after second and third trimester chemotherapy exposure. [38,40,45-49] However, caution remains warranted as after organogenesis, the eyes, genitalia, the hematopoietic system and central nervous system are still vulnerable to exposure.[5]

Results of cohort studies appear to be inconsistent with regard to the effect on birth weight, with some studies revealing an increased risk for small for gestational age (SGA) fetuses[13,50] and others finding no different results[6,10,51,52] or even a higher incidence of large for gestational age fetuses.[8,10] Variations in management during pregnancy, treatment modalities and the type of cancer diagnosed in the studied populations most likely explains this inconsistency. Based on the largest cohorts, antenatal cancer treatment is associated with low birth weight. In the study of Cardonick et al. 2010, 8 children (6.9%) were small for gestational age.[45] No significant differences were found for gestational age at delivery or birth weight according to the treatment given during pregnancy. Another cohort study in 2017 assessed the neonatal outcome of 61 infants prenatally exposed to chemotherapy.[48] The overall rate of small for gestational age was 32%, independent whether or not chemotherapy was administered during pregnancy. The largest cohort study to date evaluated the outcome of 955 neonates born after a cancer diagnosis during pregnancy: 21% of the fetuses were born SGA.[4] Maternal age, cytotoxic agents and type of malignant disease were defined as risk factors. Fetuses that were exposed to platinum-based chemotherapy during pregnancy were at highest risk for SGA.

The exact etiology of SGA and stillbirth in pregnancies complicated with a cancer diagnosis needs further research. As some cytotoxic drugs have several toxic properties and cross the placenta, fetal growth may be directly affected. Similarly, it appears that stillbirth and preterm SGA are stronger associated with maternal cancer diagnosed during the second trimester of pregnancy, which is more likely treated than cancers diagnosed in the other trimesters.[13] Also chemotherapy may alter placental growth factors. Whole transcriptome sequencing and immunohistochemical analysis reveal an increase in oxidative DNA damage in chemotherapy-exposed placentas.[53] However, cancer treatment might not be the only explanation for increased neonatal risks. Other factors related to cancer diagnosis such as maternal nutrition, anemia, thrombosis, maternal age and maternal (psychological) stress might affect fetal growth.[54-56] That cancer itself may adversely affect fetal growth is proven by the association between preterm SGA and cancer diagnosis within 3 months after delivery, as a likely incipient yet untreated cancer during pregnancy.[57,58] Fortunately, it seems that these SGA children show compensatory growth in the first months after birth.[38,47]

The literature is inconsistent regarding the association of cancer during pregnancy and neonatal death. Most population-based linkage studies found no increased risk.[8,11,14,52,59]

In contrast, a recent large Swedish nationwide cohort study concluded that maternal cancer diagnosis was associated with an increased risk of adverse neonatal outcomes, including preterm SGA birth, stillbirth and neonatal mortality.[57] Also postnatal cancer diagnosis was found to be associated with preterm SGA and neonatal mortality, but not with stillbirth. Information on treatment modalities during or after pregnancy was lacking. The association between SGA and stillbirth is not surprising as they share etiological factors, including intrauterine malnourishment[60] and SGA itself is a major determinant of stillbirth, especially preterm stillbirth.[61] In order to optimize the timing of oncological treatment or due to maternal deterioration, iatrogenic preterm delivery is common in pregnancies complicated by cancer. The authors suggested that 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.[62]

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.[46] NICU admission was associated with exposure to taxanes and was more likely after a diagnosis of gastrointestinal or cervical cancer during pregnancy.

In a case series of 50 neonates prenatally exposed to chemotherapy for acute leukemia in the last month of pregnancy, 33% were cytopenic at birth.[63] Delivery should be avoided during the maternal nadir period to prevent myelosuppression and the additional risk of sepsis.[5] Especially in preterm babies administration of chemotherapy shortly before delivery might not have been eliminated because of the limited ability of immature liver and kidney function to metabolize cytotoxic drugs. Delay of delivery for 2-3 weeks after chemotherapy allows for placental drug excretion.

Pediatric outcome

The long term outcome of children exposed to maternal malignancy and its treatment on general health, cardiologic, cognitive, behavioral and neurological development is still a concern since data on these long term effects are scarce. Table 4 gives an overview of the published series on prenatal cancer exposed children.[38,46,47,63-68]

In adults and children treated with anthracyclines, short-and long-term cardiotoxic effects were reported.[69] An animal study with pregnant rats displayed no acute cardiotoxicity in the offspring in response to doxorubicin, despite detectable drug levels (6.2 ±3.2% of maternal concentration) in the fetal concentration, in contrast to an impaired maternal left ventricular function and a doxorubicin-induced decrease in maternal body weight.[70] Cardiologic assessment in ten anthracycline-exposed pregnant patients showed no significant short-term effect on both maternal and fetal cardiac function.[71] Cardiac function in 65 children prenatally exposed to chemotherapy was not affected at the age of 1 to 18 years, compared to age- and sex-matched controls.[38] Electrocardiographic results revealed

no arrhythmia or conduction abnormalities, although a higher heart rate (median 109, range 61-152) was observed in the study group. 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. Some of the heart-rate dependent diastolic variables were significantly different between the patient and control group. Mitral valve E velocity was lower, mitral valve A velocity was shorter and isovolumetric relaxation time was shorter in the study group. However, all measurements were still within the normal range. A normal cardiac function was confirmed among 47 prenatal exposed children at 36 months of age.[47] Furthermore, the use of chemotherapy during pregnancy in 81 children with mean age of 17 years old (range 9.3-29.5) did not show any clinical or echocardiogram evidence of late cardiac toxicity.[67]

Table 4: Current published literature on outcome of children prenatally exposed to cancer or cancer treatment

Reference	No. of children	Year of publication	Age at follow-up [mean(range)]	Country	Type of cancer	Tests
[63], Reynoso et al	7	1987	1-17 years	Toronto, Canada	Acute leukemia	Different per case: Clinical examination for growth and development Cognition: information regarding intellectual performance and intelligence test in 1/7 cases.
[64], Aviles et al*	84	2001	18.7 (6-29) years	Mexico	Hematological cancers	Complete neurological and psychological examination Complete blood count Cardiac function: echocardiography Cognition: information regarding school performance
[44], Hahn et al	40	2006	2 to 157 months	USA, Texas	Breast cancer	Cognition / Physical: follow-up survey
[67], Aviles et al*	81	2006	17.1 (9.3-29.5) years	Mexico	Hematological cancers	Clinical examination Cardiac function: echocardiography
[65], Aviles et al*	54	2012	22.4 (3.8-32.0) years	Mexico	Hematological cancers	Clinical examination Complete blood count Cardiac function: echocardiography Cognition: teachers questionnaire and Intelligence Wechsler test Chromosomal examination

Table 4: Current published literature on outcome of children prenatally exposed to cancer or cancer treatment (continued)

Reference	No. of children	Year of publication	Age at follow-up [mean(range)]	Country	Type of cancer	Tests
[38], Amant et al	70	2012	22.3 (16.8-211.6) months	Belgium The Netherlands Czech republic	All types	Clinical neurological examination Cognition: Bayley Scales of Infant Development Behavior: Child Behavior check list (CBCL) Audiometry test from the age of 5 Cardiac function: electrocardiography and echocardiography
[46], Murthy et al	50	2014	7 (<1 to 21) years	USA, Texas	Breast cancer	Cognition / Physical: follow-up survey
[68], Cardonick et al	22 children not chemo-exposed 35 children chemo-exposed	2015	4.9 years (no chemo-exposed) and 4.5 years (chemo-exposed) Range: 18 months – 10.4 years	USA	All types	Cognition: Bayley Scales of Infant Development (age 18-42 months), The Wechsler Preschool and Primary Scale of Intelligence-Revised (age 3-7 years), The Wechsler Intelligence Scale for Children and individual Achievement Test (≥7 years) Behavior: Child Behavior Checklist (CBCL)
[47], Amant et al	129 129 control children**	2015	82 (12-42) months	Belgium The Netherlands Italy Czech Republic	All types	Cognition: Bayley Scales of Infant Development Cardiac function: electrocardiography and echocardiography Clinical neurological examination
[66], Aviles et al*	44 chemo exposed	2018	120.4 (48-299) months,	Mexico	Hodgkin Lymphoma (early stage)	Cognition: Psychological test, behavior development and scholar attendance Cardiac function: echocardiography

For Cognitive data: compared to (gestational) age-, sex and country-matched (no cancer exposed) controls.
* Data from the same research groups or medical centers might be used in different studies.
**For cardiac data compared to age- and sex-matched (no cancer-exposed) controls.

As the central nervous system continues to develop after the first trimester and throughout pregnancy, chemotherapy administered in the second or third trimester of pregnancy may affect neurocognitive development. Cognitive problems may become more apparent with increasing age as tasks become more complex and challenging for the child's cognitive abilities. In a study that followed 84 children until an age of 18.7 years, a normal physical, neurological and neurocognitive development was found.[64] Another study on the long-term outcome of 70 children exposed to chemotherapy in utero with a median age of 22.3

months (range 16.8 months – 17.6 years) reported normal neurodevelopment.[38] Remarkably, 29% exposed children had an increased score for internalizing, externalizing or total problems behaviors compared to the general population. In addition, 50 pregnant breast cancer patients treated with 5-fluorouracil, doxorubicin and cyclophosphamide (FAC) completed a post neonatal health questionnaire. Fetal exposure to FAC was not associated with serious adverse events or short-term health concerns and cognitive abnormalities for offspring.[46] The largest cohort study up to date comprehends 96 children exposed to chemotherapy after the first trimester with a median follow-up of 22 months.[47] These children were compared with healthy controls, matched for gestational age at delivery and test age. The cognitive, cardiac and general development of children who were exposed to chemotherapy did not differ significantly from the control group. These results suggest that chemotherapy had no clear adverse short term effect on postnatal growth or on cognitive or cardiac function. In addition, this study found that preterm birth was an independent predictor of poorer cognitive outcome in both the study and control group.

Ototoxicity is a known complication of platinum-based chemotherapy and cisplatin carries the greatest risk.[72,73] Cisplatin has a low molecular weight and has the potential to easily cross the placenta.[23] Few cases of hearing loss after prenatally exposure to cisplatin have been reported.[74,75] Amant et al. assessed auditory functioning in 21 children between 6 and 18 years who were exposed to platinum-based treatment during pregnancy. While 18 children showed no abnormalities, 3 children reported hearing loss. In reported cases, infection, the use of aminoglycosides and neurodevelopmental problems in these children were possible confounding factors.[38] 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.[76] 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.[64] 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.

CONCLUSION

Increased awareness of the feasibility of cancer treatment during pregnancy results in more pregnant women receiving oncological treatment and more children prenatally exposed to cytotoxic drugs. Acknowledgement of possible obstetric and neonatal risks in this population is of extreme importance, as cancer in pregnancy is related to maternal and fetal morbidity. A multidisciplinary approach and follow-up in an experienced center with

high risk obstetric unit is therefore recommended. Overall, prenatal exposure to maternal cancer and cytotoxic treatment does not appear to impair physical, cardiologic, cognitive and neurological development. However iatrogenic preterm delivery should be prevented when possible. Moreover, more thorough and longer follow up is needed to delineate the safety of both the children and their mothers. In order to provide more long-term evidence, INCIP set up a multidisciplinary network to follow the development of children prenatally exposed to cancer or cancer treatment until the age of 18 years and beyond. Specialists with a special interest in cancer and pregnancy are invited to participate in the worldwide registry of INCIP.

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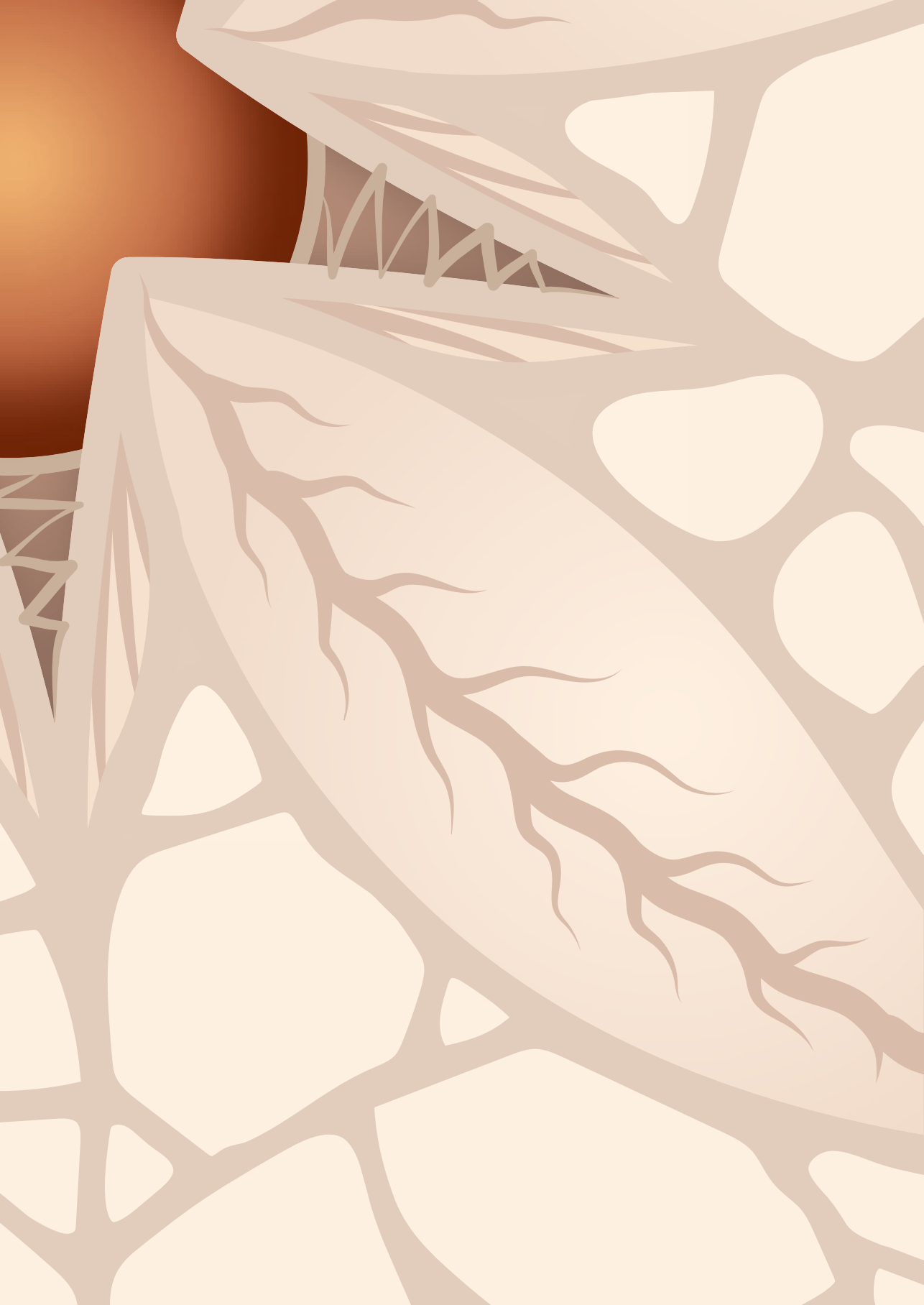

Chapter 3.

Association of chemotherapy timing in pregnancy with congenital malformation

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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).[1] 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).[1,2] 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 birth weight 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 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.[3]

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.

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]).

Table 1: Clinical characteristics of patients

Characteristics	Patients, No. (%)		
	Total (N = 755)	Gestational age at chemotherapy exposure	
		< 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)

Table 1: Clinical characteristics of patients (continued)

Characteristics	Patients, No. (%)		
	Total (N = 755)	Gestational age at chemotherapy exposure	
		< 12 wk (n = 29)	Exposure ≥ 12 weeks of gestation (n=726)
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 during pregnancy (first trimester)	18 (2.4)	1 (3.4)	17 (2.3)
Surgery during pregnancy (first trimester)	315 (41.7)	12 (41.4)	303 (41.7)
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)

Table 1: Clinical characteristics of patients (continued)

Characteristics	Patients, No. (%)		
	Total (N = 755)	Gestational age at chemotherapy exposure	
		< 12 wk (n = 29)	Exposure ≥ 12 weeks of gestation (n=726)
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.

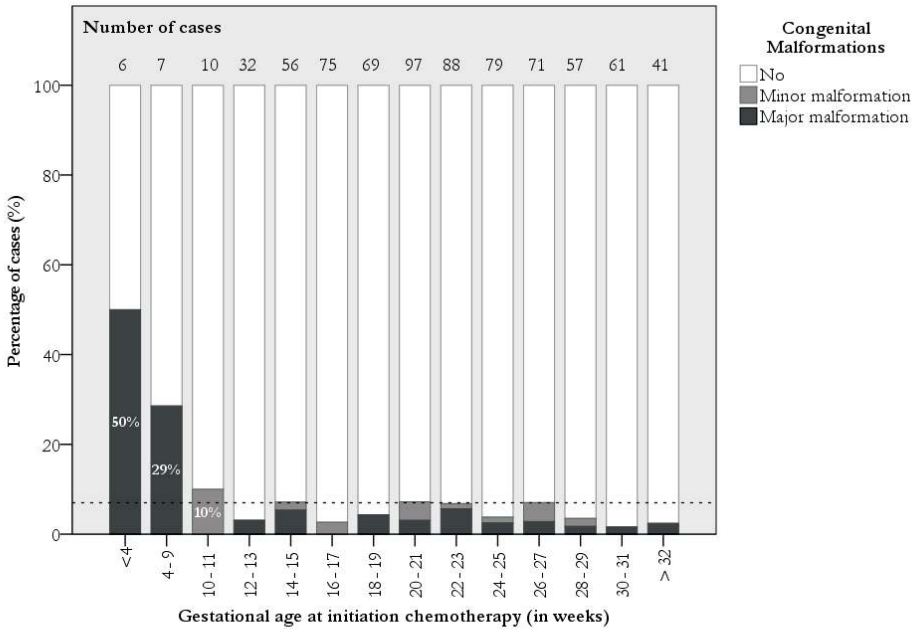

Figure. Frequency of congenital anomalies according to gestational age at first chemotherapy exposure
The dotted line indicates 7%, the maximum percentage of congenital anomalies (both minor and major) according to gestational age at initiation of chemotherapy, from 12 weeks onwards.

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). 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).[4-6] 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.[1] 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.[1] 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.[7,8] 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.[1] 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.[9] 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.[10,11] 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.[12,13] 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.[14] 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.[2] 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.[15]

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.

CONCLUSIONS

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.

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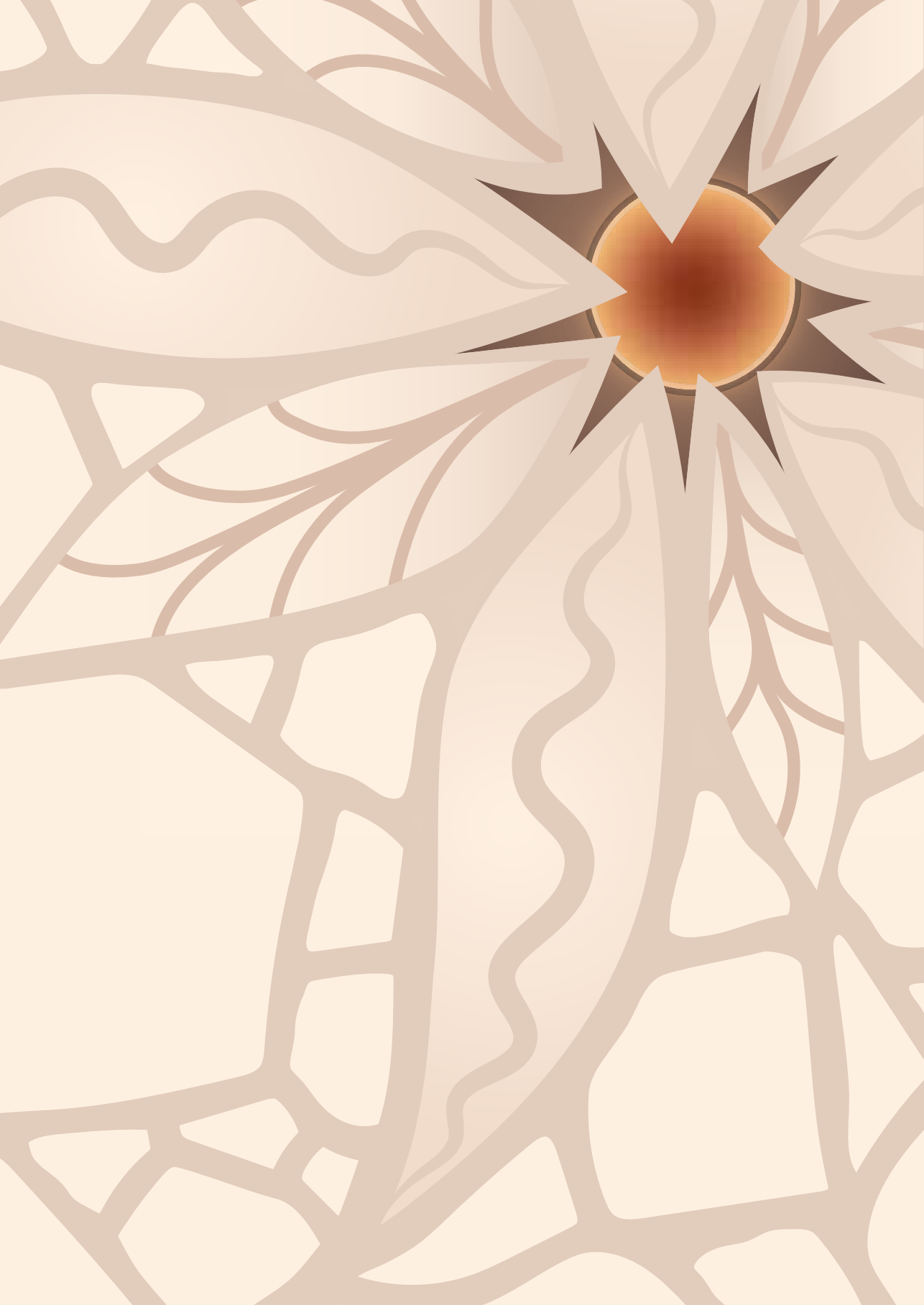

Chapter 4.

Pediatric outcome at age 6 after maternal cancer diagnosed during pregnancy

Child development at 6 years after maternal cancer diagnosis and treatment during pregnancy

Data describing child development at 6 years after maternal cancer diagnosis and treatment during pregnancy

Executive functioning in 6 year old children exposed to chemotherapy in utero

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ABSTRACT

Background

Data on the long-term effects of prenatal exposure to maternal cancer and its treatment on child development are scarce.

Methods

In a multicenter cohort study, the neurologic and cardiac outcomes of 6-year-old children born to women diagnosed with cancer during pregnancy were compared to the outcome of children born after an uncomplicated pregnancy. Assessment included clinical evaluation, comprehensive neuropsychological testing and electro- and echocardiography.

Results

In total, 132 study children and 132 controls were included. In the study group, 97 children (73.5%) were prenatally exposed to chemotherapy (alone or in combination with other treatments), 14 (10.6%) to radiotherapy (alone or in combination), 1 (0.8%) to trastuzumab, 12 (9.1%) to surgery alone and 16 (12.1%) to no treatment. Although within normal ranges, statistically significant differences were found in mean Verbal IQ and visuospatial long-term memory, with lower scores in the study versus control group (98.1, 95% CI 94.5-101.8, vs 104.4, 95% CI 100.4-108.4, P=0.001, Q<0.001 (Q refers to the false discovery rate adjusted P value), and 3.9, 95% CI 3.6-4.3, vs 4.5, 95% CI 4.1-4.9, P=0.005, Q=0.045, respectively). A significant difference in diastolic blood pressure was found, with higher values in chemotherapy-exposed (61.1, 95% CI 59.0 to 63.2) versus control children (56.0, 95% CI 54.1 to 57.8) (P<0.001, Q<0.001) and in a subgroup of 59 anthracycline-exposed (61.8, 95% CI 59.3 to 64.4) versus control children (55.9, 95% CI 53.6 to 58.1) (P<0.001, Q=0.02).

Conclusions

Children prenatally exposed to maternal cancer and its treatment are at risk for lower Verbal IQ and visuospatial long-term memory scores and for higher diastolic blood pressure, but other cognitive functions and cardiac outcomes were normal at the age of 6 years.

INTRODUCTION

Cancer during pregnancy is a challenge, as the health of both mother and fetus have to be considered in therapeutic decision making. Over the past 20 years, clinical management of pregnant cancer patients has evolved with a higher number of patients receiving treatment during pregnancy, less terminations of pregnancy and less medically induced preterm deliveries.[1] Cancer treatment may have acute and/or chronic side effects on the fetus, including neurotoxicity and cardiotoxicity, as chemotherapy may cross the placenta in varying amounts.[2,3] Additionally, cancer may be accompanied by maternal stress, inflammatory reactions, exposure to radiation, anesthesic agents and other medications, potentially influencing fetal development. Notwithstanding, data on the short- and long-term impact on fetal development are still limited.[4]

Our group previously published two studies, documenting reassuring health status, cognitive and cardiac outcomes at a median age of 22 months.[5,6] However, cognitive problems may become more apparent at school-age and can be more accurately evaluated at older ages. Moreover, cardiac problems may develop many years after chemotherapy exposure.[7,8] Therefore, this study aims to investigate the health status, cognitive and cardiac outcome of 6-year-old children prenatally exposed to maternal cancer and its treatment, and in particular, to chemotherapy.

MATERIAL AND METHODS

Study participants

This is a multicenter cohort study including children born to women diagnosed with cancer during pregnancy (with or without treatment during pregnancy) (study group). At predefined ages (1.5, 3, 6, 9, 12, 15 and 18 years), the children are invited for follow-up. In this study, we compare the outcome of 6-year-old children from the study group with children born after an uncomplicated pregnancy (control group). Study children were identified and enrolled prospectively (during pregnancy or between birth and 6 years) and evaluated at 6 referral centers in Belgium, the Netherlands, the Czech Republic and Italy, all members of the International Network on Cancer, Infertility and Pregnancy (INCIP). Control children were identified and enrolled at the age of 6 years. For the neurocognitive tests and health examination, the study and control children were 1:1 matched for country, gender, age, gestational age at birth and language of the tests. For the cardiac examinations, children were 1:1 matched for gender and age. The study design and recruitment are summarized in Figure 1. Details on the recruitment and exclusion criteria are provided in the Methods section in the data article. Ethical approval was obtained by each institution

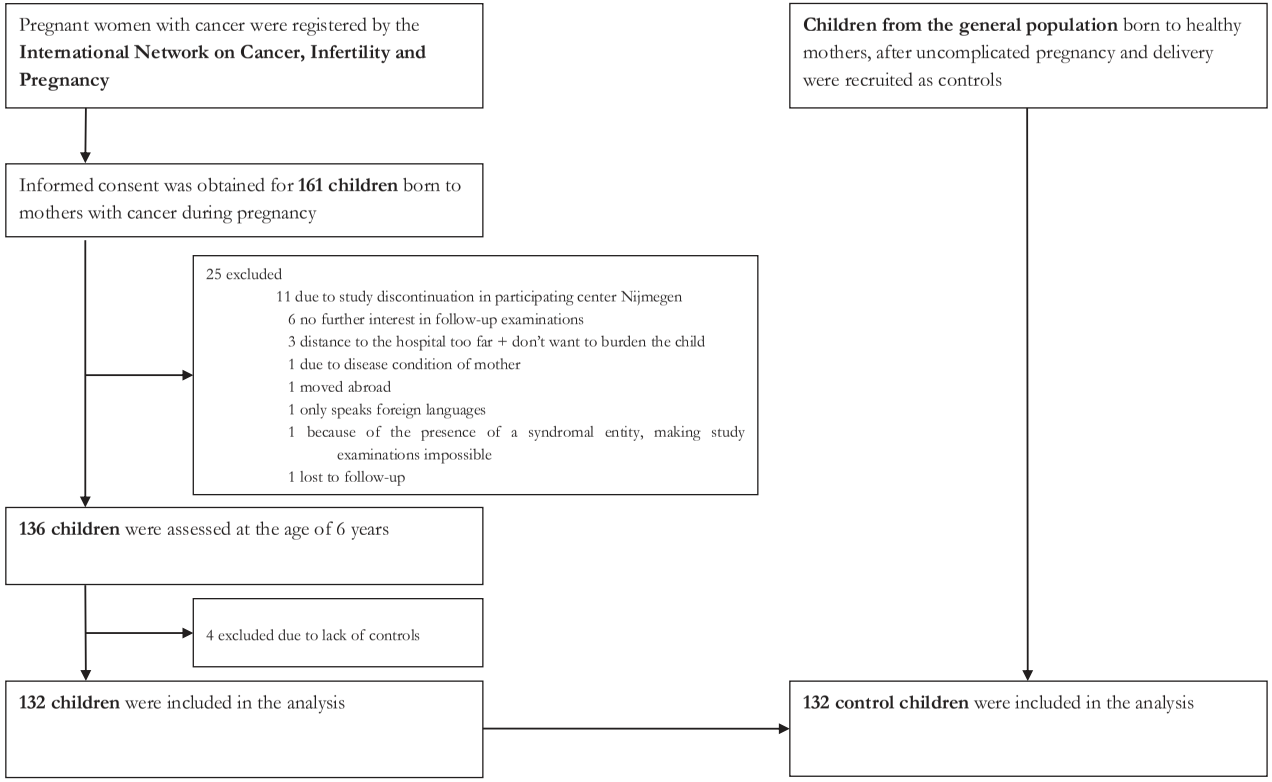


Figure 1. Study design and recruitment

This cohort of 132 children evaluated at the age of 6 years includes 83 children who underwent cognitive evaluation and 28 children who underwent cardiac examinations in our previously published 1.5-3 years cohort study.[6] The results of 12 children at the age of 6 years were previously published,[5] whereas 120 children underwent new testing. Longitudinal analyses will be performed when we reach our sample size in the oldest age group.

and the parents of each child provided written informed consent to participate. The full study protocol is available at http://www.cancerinpregnancy.org/study-protocols.

Study testing and outcomes

Oncological, obstetrical and neonatal data were collected. Cognitive development was examined using a comprehensive neuropsychological test battery to assess intelligence, memory, attention and behavior problems (Table 1).

Table 1. Neuropsychological outcome measures

Outcome measure	Test used
Primary outcome	
Full Scale Intelligence	Wechsler Preschool and Primary Scale of Intelligence – third edition (WPPSI-III)[26]
Secondary outcomes	
Verbal Intelligence, Performance Intelligence and Processing Speed	Wechsler Preschool and Primary Scale of Intelligence – third edition (WPPSI-III)[26]
Verbal and visuospatial memory span, visuospatial short- and long-term memory, verbal working memory and short- and long-term memory for faces	Children's Memory Scale (CMS)[27]
Alertness, divided attention, selective attention and response inhibition	Amsterdam Neuropsychological Tasks (ANT)[28]
Internalizing and externalizing behavior problems	Child Behavior Checklist (CBCL)[29]

Cardiac evaluation included a 12-lead electrocardiogram and an echocardiographic examination performed according to American Society of Echocardiography guidelines. The primary cardiac outcome was left ventricular shortening fraction measured by M-Mode. Secondary outcomes included the cardiac chamber dimensions (Left and Right Ventricular End-diastolic Diameter, Left Ventricular Posterior Wall Thickness, Interventricular Septum Thickness), Left Ventricular ejection fraction, the mitral valve E- and A-velocity and E/A ratio, tissue Doppler imaging velocities at the left and right ventricular wall and interventricular septum, and the longitudinal and circumferential 2D-strain measurements by speckle-tracking echocardiography.

Study children underwent a clinical neurological and general pediatric examination and the parents filled out a health questionnaire. The incidence rates of health problems were considered as secondary outcomes.

Details on the neuropsychological and echocardiographic protocol and the health questionnaire are provided in the Methods section in the data article.

Statistical analysis

We converted raw scores into standardized scores for the intelligence tests and behavior questionnaires, according to normative data for each country provided by the test. For the

memory tests, raw subtest scores were used. Reaction times and percentage of errors were obtained for the attention tasks. Univariate analyses of covariance (ANCOVA) were used to investigate between-group differences in cognitive outcome and behavior with education levels of parents as covariates. A subgroup analysis was performed in chemotherapy-exposed children versus controls. Additionally, the incidence of behavior problems was compared to matched controls for children whose mothers died and for those with surviving mothers. Posthoc, Verbal IQ was compared between children exposed to different types of chemotherapy and matched controls and between children whose mothers died versus those with surviving mothers and their matched controls. The associations between cognitive outcome and gestational age or the number of chemotherapy cycles were investigated using Pearson correlations. The Spearman's rank-correlation coefficient was used to investigate the relationship between cognitive outcome and the estimated fetal dose of radiation.

Echocardiographic measures were obtained in three cardiac cycles and averaged. Between-group differences were investigated using univariate analysis of variance (ANOVA). A subgroup analysis was performed in anthracycline-exposed children versus controls.

Q values, which represent false discovery rate adjusted P values, were calculated in order to correct for multiple testing.[9] A two-sided Q value of less than 0.05 was considered to indicate statistical significance.

RESULTS

Characteristics of the children

In total, 132 children (including five pairs of dizygotic twins) born to mothers diagnosed with cancer during pregnancy were included, of whom 88 from Belgium, 25 from the Netherlands, 12 from Italy and 7 from the Czech Republic. During pregnancy, 97 children (73.5%) were exposed to chemotherapy (alone or in combination with other treatments), 14 (10.6%) to radiotherapy (alone or in combination), 1 (0.8%) to trastuzumab, 12 (9.1%) to surgery alone and 16 children (12.1%) were born to mothers not treated during pregnancy (Table 2). Twenty-five mothers (19.7%) died before the child was 6 years old. Additional information about the maternal cancer types and specific treatments is provided in Tables 1 and 2 and eTable 1 to 6, all in the data article.

In general, demographic and perinatal characteristics were comparable between the study and control group (Table 3 and eTable 7-10 in the data article).

Table 2. Cancer treatment during pregnancy for all children and those categorized as small for gestational age in singleton pregnancies

Cancer treatment	**All children (N=132)** Number (%)	**Small for gestational age (N=18)** Number (% of children with treatment, excluding twins)
Surgery	12 (9.1)[a]	1 (10.0)
Chemotherapy	38 (28.8)	9 (23.7)
Radiotherapy	1 (0.8)	0 (0.0)
Surgery and chemotherapy	51 (38.6)[a]	5 (11.1)
Surgery and radiotherapy	5 (3.8)	2 (40.0)
Surgery, chemotherapy, and radiotherapy	8 (6.1)[a]	0 (0.0)
Trastuzumab	1 (0.8)	0 (0.0)
No treatment	16 (12.1)	1 (6.3)

[a]One pair of twins was exposed to surgery alone, three pairs of twins to surgery and chemotherapy, and one pair of twins to surgery, chemotherapy and radiotherapy.

Table 3. Demographic characteristics of the children included in the cognitive and health examinations

Characteristic	**Cancer in pregnancy group (N=132)**	**Control group (N=132)**	**P value**
Median age (range) - years	6.1 (4.8-7.9)	6.2 (4.7-7.7)	0.29
Median gestational age (range) - weeks	36.1 (27.4-40.7)	36.1 (28.6-41.0)	0.65
Median birth weight (range) - grams	2705 (720-4200)	2713 (1025-4400)	0.73
Median maternal age at birth of this child (range) - years	33 (19-44)	31 (20-46)	0.02
Sex – number (%)			1.00
Male	71 (53.8%)	71 (53.8%)	
Female	61 (46.2%)	61 (46.2%)	
Race – number (%)[a]			0.27
White	115 (87.1%)	119 (90.2%)	
Black	11 (8.3%)	5 (3.8%)	
Other	6 (4.5%)	8 (6.1%)	
Highest level of education of parents – number (%)[b]			
Mother			0.07
Primary school	5 (3.8%)	2 (1.5%)	
Secondary school	52 (39.4%)	34 (25.8%)	
Bachelor	42 (31.8%)	53 (40.1%)	
Master's degree or higher	33 (25.0%)	41 (31.1%)	
Unknown	0 (0.0%)	2 (1.5%)	

Table 3. Demographic characteristics of the children included in the cognitive and health examinations (continued)

Characteristic	Cancer in pregnancy group (N=132)	Control group (N=132)	P value
Father			0.69
Primary school	7 (5.3%)	5 (3.8%)	
Secondary school	58 (43.9%)	51 (38.6%)	
Bachelor's degree	33 (25.0%)	32 (24.2%)	
Master's degree or higher	32 (24.2%)	39 (29.5%)	
Unknown	2 (1.5%)	5 (3.8%)	

[a]Race was self-reported by the parents.

[b]The highest level of education is presented according to the European educational system. A bachelor's degree is earned at both traditional universities and nonuniversity institutions of higher education and requires between three and four years of full-time study. A master's degree is earned at university and requires one to two years of full-time study after a bachelor's degree.

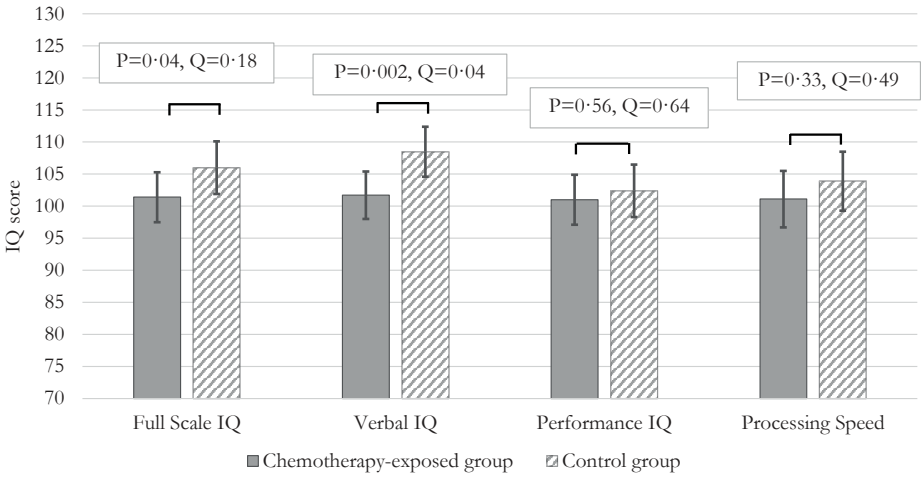
Perinatal outcome and growth

In the cancer group, median gestational age at birth was 36.1 weeks (range 27.4-40.7) and median birth weight was 2705g (range 720-4200). Eighty children (60.6%) were born preterm (vs 6.8-8.0% in the participating countries)[10], of whom 8 (6.1%) very preterm (27.0-31.9 weeks gestational age), 16 (12.1%) moderately preterm (32.0-33.9 weeks) and 56 (42.4%) late preterm (34.0-36.9 weeks), and 52 children (39.4%) were born at term (37.0 weeks or later). The number and type of the registered congenital malformations were not different from the general population (eTable 11 in the data article). After exclusion of twins, 18/121 children (14.9%) in the study group were born small for gestational age (SGA, i.e., a birth weight below the tenth percentile of gender and gestational age matched children) versus 7/119 (5.9%) in the control group (eTable 12 in the data article). Biometric data at 6 years were comparable between the groups (eFigure 1 and 2).

Cognitive development and behavior

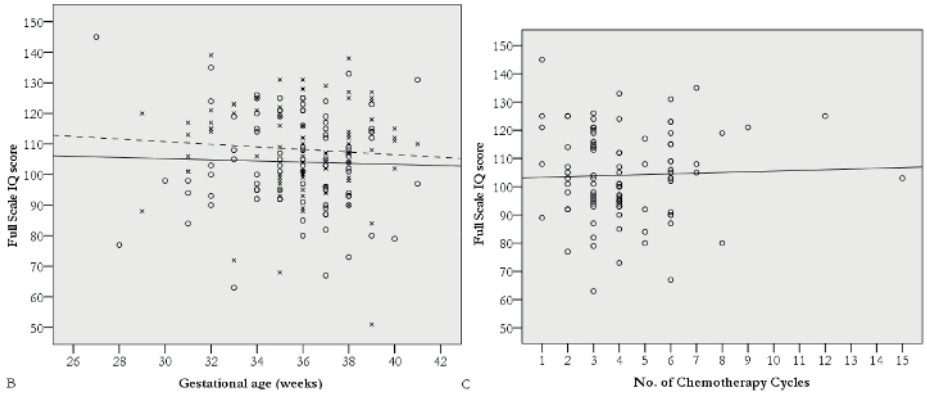
Median age at cognitive evaluation was 6.1 and 6.2 years in the study and control group respectively. The difference in estimated marginal means of the primary outcome Full Scale IQ was not statistically significant between the study group (98.9, 95% CI 95.2 to 102.6) and the control group (103.0, 95% CI 98.9 to 107.0) (P=0.03, Q=0.15) (eTable 13 and eFigure 3 in the data article) or between the subgroup of chemotherapy-exposed children (101.4, 95% CI 93.7 to 109.1) and controls (106.0, 95% CI 98.0 to 114.0) (P=0.04, Q=0.17) (Figure 2A and eTable 14 in the data article). Full Scale IQ was not related to gestational age in the chemotherapy-exposed group (r=-0.04, P=0.74) and the control group (r=-0.08, P=0.43) (Figure 2B), to the number of chemotherapy cycles (r=0.04, P=0.74) (Figure 2C) or to the dose of radiation (r=0.19, P=0.52) (eFigure 4 in the data article).

Figure 2. Cognitive outcome



2A. Comparison of the mean Full Scale IQ, Verbal IQ, Performance IQ and Processing Speed between the chemotherapy-exposed group and the control group

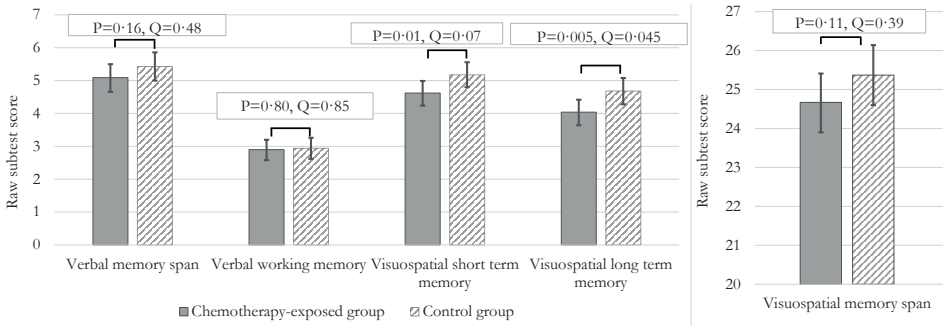
The mean of standardized IQ-scores is 100 with a standard deviation of 15 and scores between 90 and 110 are considered average. Higher scores indicate more advanced development.



2B. The relation between Full Scale IQ and gestational age at birth (in weeks) for the chemotherapy-exposed and control group

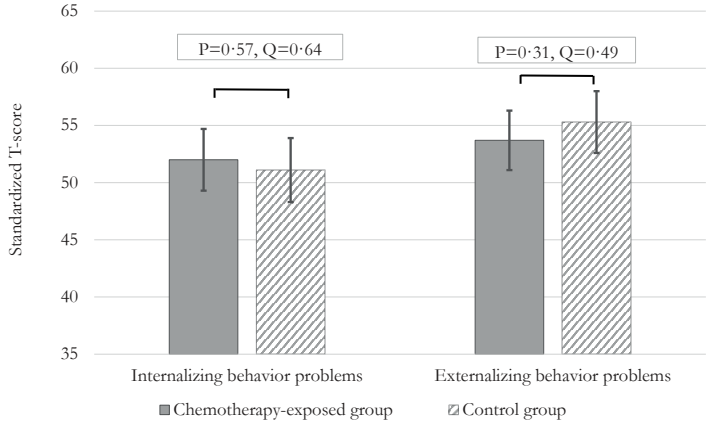
Values of children from the chemotherapy-exposed group are represented by circles, those of children from the control group are represented by crosses. Mean values (as calculated by linear regression) are indicated by a solid line for the chemotherapy-exposed group and a dashed line for the control group.

2C. The relation between Full Scale IQ and the number of chemotherapy cycles administered during pregnancy



2D. Comparison of the raw memory scores from the subtests of the Children's Memory Scale between the chemotherapy-exposed group and the control group

Verbal memory was measured using the subtest Numbers (range of scores between 0-14 for Numbers Forward (verbal memory span) and 0-12 for Numbers Backward (verbal working memory)). Visuospatial short- and long-term memory were measured using the subtest Dot Locations (range 0-6). Visuospatial memory span was measured using the subtest Picture Locations (range 0-30). Higher scores indicate more advanced memory skills.



2E. Comparison of the standardized T-scores for internalizing and externalizing behavior problems on the Child Behavior Checklist between the chemotherapy-exposed group and the control group

The mean of standardized T-scores is 50 with a standard deviation of 15. Higher scores indicate more behavior problems.

Figures 2A, 2D, 2E: The figures show estimated marginal means with standard errors of the means for each group and variable. Raw P values and false discovery rate adjusted P values (Q values) are presented

With regard to the secondary outcomes, the difference in estimated marginal means of Verbal IQ was statistically significant, with lower values in the study group (98.1, 95% CI 94.5 to 101.8) compared to the control group (104.4, 95% CI 100.4 to 108.4) (P=0.001, Q<0.001) and in chemotherapy-exposed children (101.7, 95% CI 94.3 to 109.0) compared to their matched controls (108.5, 95% CI 100.8 to 116.1) (P=0.002, Q=0.03). Posthoc, we evaluated the possible impact of death of the mother on Verbal IQ. The size of the between-group difference in Verbal IQ was larger in children whose mother died (15.1 IQ points), compared to those with surviving mothers (4.9 points) (eTable 16 in the data article). There were no statistically significant between-group differences in Performance IQ or Processing Speed (Figure 2A and eTables 13 and 14 in the data article). With regard to memory, the difference in estimated marginal means of visuospatial long-term memory was statistically significant, with lower values in the study group (3.9, 95% CI 3.6 to 4.3) compared to the control group (4.5, 95% CI 4.1 to 4.9) (P=0.005, Q=0.045) and in chemotherapy-exposed children (4.0, 95% CI 3.3 to 4.8) compared to their controls (4.7, 95% CI 3.9 to 5.5) (P=0.005, Q=0.045) (eTables 17 and 18 in the data article). No statistically significant differences were found in memory span, short-term memory, attention or behavior problems between the study and control group and between chemotherapy-exposed and control children (Figure 2D-2E) (eTables 17-22 in the data article). The differences in internalizing and externalizing behavior problems were also not statistically significant for study children whose mothers died and those with surviving mothers compared to their matched controls (eTable 23 in the data article).

Cardiac evaluation

Cardiac evaluation was performed in 78 chemotherapy-exposed children and matched controls. Median age was 6.1 and 6.2 years in the chemotherapy-exposed and control group, respectively. No statistically significant between-group differences in body surface area, heart rate and systolic blood pressure were found. The difference in means of diastolic blood pressure was statistically significant, with higher values in chemotherapy-exposed (61.1, 95% CI 59.0 to 63.2) versus control children (56.0, 95% CI 54.1 to 57.8) (P<0.001, Q<0.001) and in a subgroup of 59 anthracycline-exposed (61.8, 95% CI 59.3 to 64.4) versus control children (55.9, 95% CI 53.6 to 58.1) (P<0.001, Q=0.02) (Table 4 and eTable 24 in the data article). Electrocardiographic evaluation did not reveal rhythm or conduction abnormalities. On echocardiographic examination, no structural abnormalities were detected in any of the children. The difference in means of the primary outcome left ventricular shortening fraction was not statistically significant between chemotherapy-exposed and control children. Additionally, no statistically significant between-group differences were found in secondary outcomes.

Table 4. Echocardiographic data and other measurements of cardiac function

Measurement	Chemotherapy-exposed group (N=78)					Control group (N=78)				Type 3 test of fixed effects			
	No.	Mean	S.E.	95% CI		Mean	S.E.	95% CI		F	P value	Q value	Partial eta squared
				Lower	Upper			Lower	Upper				
Body-surface area (m^2)	153	0.84	0.01	0.83	0.86	0.84	0.01	0.82	0.86	0.05	0.83	0.95	0.000
Blood pressure (mm Hg)													
Systolic	134	102.61	1.23	100.19	105.04	99.71	1.05	97.63	101.80	3.22	0.08	0.30	0.024
Diastolic	134	61.11	1.08	58.97	63.24	55.97	0.93	54.14	57.81	13.02	<0.001	<0.001	0.090
Heart rate (beats/min)	155	82.48	1.35	79.82	85.15	82.36	1.34	79.71	85.01	0.004	0.95	0.99	0.000
Left ventricular shortening fraction (%)	156	36.31	0.50	35.33	37.30	37.14	0.50	36.16	38.13	1.38	0.24	0.60	0.009
Left ventricular ejection fraction (%)	156	66.84	0.63	65.60	68.09	67.93	0.63	66.68	69.17	1.48	0.23	0.60	0.010
End-diastolic diameter (cm)													
Left ventricular	156	3.59	0.03	3.53	3.65	3.65	0.03	3.59	3.71	2.18	0.14	0.49	0.014
Right ventricular	152	1.57	0.03	1.52	1.62	1.60	0.03	1.55	1.65	0.77	0.38	0.71	0.005
Left ventricular posterior-wall thickness (cm)	156	0.53	0.01	0.51	0.55	0.54	0.01	0.52	0.55	0.07	0.80	0.95	0.000
Interventricular septum thickness (cm)	156	0.52	0.01	0.51	0.54	0.54	0.01	0.53	0.56	3.73	0.06	0.26	0.024
Mitral valve E velocity (m/s)	153	1.01	0.02	0.98	1.04	1.07	0.02	1.04	1.10	6.60	0.01	0.13	0.042
Mitral valve A velocity (m/s)	152	0.53	0.01	0.50	0.55	0.57	0.01	0.55	0.60	5.95	0.02	0.13	0.038
Mitral valve E/A ratio	152	1.98	0.05	1.88	2.09	1.95	0.05	1.85	2.05	0.23	0.63	0.84	0.002
Basal segment of left ventricular lateral wall (cm/sec)[a]													
Peak systolic velocity	139[b]	8.90	0.25	8.41	9.40	9.09	0.23	8.63	9.54	0.30	0.59	0.84	0.002
Peak early diastolic velocity	140[b]	17.39	0.33	16.74	18.05	17.76	0.31	17.15	18.37	0.65	0.42	0.72	0.005
Peak late diastolic velocity	134 [b]	6.12	0.21	5.71	6.54	6.04	0.20	5.65	6.44	0.08	0.78	0.95	0.001

Table 4. Echocardiographic data and other measurements of cardiac function (continued)

Measurement	Chemotherapy-exposed group (N=78)					Control group (N=78)				Type 3 test of fixed effects			
	No.	Mean	S.E.	95% CI		Mean	S.E.	95% CI		F	P value	Q value	Partial eta squared
				Lower	Upper			Lower	Upper				
Basal segment of interventricular septum (cm/sec)[a]													
Peak systolic velocity	143 [b]	7.24	0.15	6.94	7.54	7.71	0.14	7.44	7.99	5.28	0.02	0.14	0.036
Peak early diastolic velocity	143 [b]	13.70	0.22	13.26	14.13	13.55	0.20	13.15	13.95	0.24	0.62	0.84	0.002
Peak late diastolic velocity	141 [b]	5.74	0.14	5.45	6.02	5.73	0.13	5.47	6.00	0.000	0.99	0.99	0.000
Basal segment of right ventricular lateral wall (cm/sec)[a]													
Peak systolic velocity	138 [b]	12.81	0.25	12.33	13.30	13.04	0.23	12.58	13.49	0.44	0.51	0.81	0.003
Peak early diastolic velocity	139 [b]	15.66	0.32	15.03	16.29	15.69	0.30	15.10	16.28	0.004	0.95	0.99	0.000
Peak late diastolic velocity	137 [b]	9.08	0.27	8.55	9.62	9.46	0.25	8.96	9.96	1.02	0.31	0.68	0.008
Global left ventricular longitudinal strain (%)	127 [b]	20.61	0.31	20.00	21.21	21.00	0.29	20.42	21.57	0.85	0.36	0.71	0.007
Global left ventricular circumferential strain (%)	109[b]	21.20	0.48	20.25	22.15	20.49	0.38	19.74	21.24	1.34	0.25	0.60	0.012

[a]Measurements were obtained with the use of tissue Doppler imaging.

[b]Data were not included when tracking could not be performed owing to poor image quality.

Health problems

The incidence of health problems and the need for surgery or care as reported by the parents were mostly comparable between the study and control group, but children from the study group were 3 times more likely to wear glasses compared to the controls (14.9 vs 5.0%) (eTable 25 in the data article). Of 14 children exposed to cisplatin, hearing loss was determined in 3 out of 8 children with available audiometric data (eTable 26 in the data article). General pediatric and clinical neurological examinations were normal in 96 out of 103 study children (93.2%) undergoing examination (eTable 27 in the data article).

DISCUSSION

In this multicenter prospective cohort study, cognitive development, health problems and growth were compared between 132 children born to mothers diagnosed with cancer during pregnancy and non-exposed matched controls and between a subgroup of 97 chemotherapy-exposed children and controls. The cardiac structure and function were also evaluated in 78 chemotherapy-exposed children and controls.

The differences in cognitive outcomes on most tests were not statistically significant between the study and control group and between the chemotherapy-exposed subgroup and controls. Especially, there were no statistically significant between-group differences in the primary outcome Full Scale IQ. Additionally, Full Scale IQ was not related to the number of chemotherapy cycles administered during pregnancy or to the estimated fetal dose of radiation. No statistically significant differences were found in Performance IQ and Processing Speed. However, children from the study group and children exposed to chemotherapy scored on average 6 points lower on Verbal IQ than their matched controls. Although the difference was statistically significant, the clinical relevance may be limited as the values were within the normal range and the between-group difference was smaller than one standard deviation (i.e., 15 IQ points). A study in preterm infants showed that increased amount of adult talk during the neonatal intensive care unit stay may contribute to higher cognitive and language outcomes at 7 and 18 months corrected age.[11] In the case of cancer during pregnancy, mother-child interactions in the neonatal period and early years of life may be more restricted due to the maternal disease and treatment or even absent in the case of maternal death. Our data support this hypothesis, as Verbal IQ was more affected in children whose mothers died than in children with surviving mothers. Furthermore, the visuospatial long-term memory score was significantly lower in the study group and in the chemotherapy-exposed subgroup compared to their matched controls, although attention, memory span and short-term memory were not affected. This is in contrast with studies on childhood cancer survivors mostly reporting working memory and attention deficits and slower information processing speed.[12]

Notwithstanding the encountered differences in Verbal IQ and visuospatial long-term memory and given the large range of cognitive functions assessed in this study, most cognitive functions were normal at the age of 6 years. This is largely consistent with our previous findings in the 1.5-3 years cohort and other studies, reporting minor to no statistically significant differences or results within normal ranges.[5,6,13-15]

In our study, 60.6% of children were born preterm, which may result from elective induction of delivery as part of treatment strategies to limit ongoing exposure of the fetus to cancer treatment or from spontaneous preterm labor which may have various cancer-related and cancer-non-related causes. In the 1.5-3 years cohort, prematurity was associated with a worse cognitive outcome.[6] This relationship was no longer present at the age of 6 years with regard to Full Scale IQ. Inconsistent findings have been reported on the long-term effects of preterm birth on cognition, especially for late preterm born children, who are the most represented preterm born children in our study.[16-19]

The cardiac evaluation in chemotherapy-exposed children was overall reassuring. No statistically significant between-group differences in cardiac dimension and global function measurements including tissue Doppler imaging and strain analyses were found and all measurements were within normal ranges. However, the diastolic blood pressure was higher in chemotherapy-exposed and anthracycline-exposed versus control children, but the clinical relevance may be limited. The overall normal cardiac findings are consistent with our previous findings in the 3-year-old cohort and other studies.[6,20-22]

The incidence of health problems was comparable between study and control children, but children from the study group were three times more likely to wear glasses than the controls. An association with cancer treatment is possible as the development of the eyes and central nervous system take place throughout the entire pregnancy and needs further investigation. Additionally, three children exposed to cisplatin were diagnosed with hearing loss. Cisplatin has also been related to ototoxicity in adults and children with cancer.[23] Ototoxicity is associated with declines on intellectual and academic performances and worse social and langauge development.[24,25] Where possible, cisplatin should be replaced by carboplatin with a more favorable toxicity profile. Long-term surveillance of auditory function of children prenatally exposed to platinum-based treatment is recommended.

Our study has some limitations. As cancer may have been present before the start of pregnancy and/or in some cases termination of pregnancy is indicated or preferred by the couple, a selection bias may be present towards a healthier subset of the eligible population and malignancies not necessitating chemotherapy during the first trimester. The results cannot be extrapolated to all types of chemotherapeutic agents and to all trimesters of pregnancy. Individual drug evaluation was not possible due to the frequent combination of different cancer treatments.

CONCLUSIONS

Children prenatally exposed to maternal cancer, the associated stress, diagnostic imaging and treatments have cognitive and cardiac outcomes within normal ranges at the age of 6 years. However, they are at risk for lower Verbal IQ and visuospatial long-term memory scores and for higher diastolic blood pressure, compared to matched controls. Additionally, they are at higher risk for need for glasses and ototoxicity in case of cisplatin exposure. In accordance to earlier studies, our data show that in many cases, the risks of maternal cancer treatment during pregnancy do not outweigh the benefit of maternal treatment delay or the need for termination of pregnancy. The results of our study will help patients to make well-informed decisions.

The data article and supplementary material related with this article can be found in the online version at doi: 10.1016/j.dib.2020.106209

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ABSTRACT

Background

Cancer treatment during pregnancy imposes a dilemma. Maternal advantage should be weighed against the potential impact of chemotherapy on child development. Recent studies in cancer survivors have shown that exposure to chemotherapeutic agents can have late adverse effects on cognitive functioning and executive functioning (EF). It is still unclear whether these late adverse effects also arise if a child is exposed to chemotherapy in utero.

Aim

To compare the development of executive functioning in 6 year old children prenatally exposed to chemotherapy (study group) and children born to healthy women after an uncomplicated pregnancy (control group).

Methods and study design

In a multicenter cohort study, the outcome on a measure of EF was compared. Study and control children were prospectively examined by means of the Behavior Rating Inventory of Executive Function (BRIEF), a health questionnaire and an intelligence test.

Results

In total 37 study children and 37 matched controls were included. In the study group, 11 children (29.7%) were exposed to chemotherapy alone, 22 children (59.5%) were exposed to chemotherapy and surgery and 4 children (10.8%) were exposed to chemotherapy, surgery and radiotherapy during pregnancy. All outcome scales of the BRIEF were within normal ranges. However, a significant between-group difference in emotional control was found.

Conclusion

Overall outcomes of EF were reassuring. However, children prenatally exposed to chemotherapy have weaker emotion regulation skills compared to their matched controls. The results underscore the need for long-term follow-up of these children.

INTRODUCTION

Cancer during pregnancy imposes a dilemma as the lives of two people have to be considered. To optimize the maternal prognosis, starting treatment during pregnancy is often inevitable. Albeit, antenatal treatment exposes the fetus to potentially toxic substances. Over the past years there is increasing awareness that antenatal chemotherapy during pregnancy is possible under well-defined circumstances.[1] It has been shown, that chemotherapy from second trimester onwards can be administered without an increased risk of congenital malformations.[2] However, data of the potential long-term effects of antenatal chemotherapy on the development of the child remain scarce.

Studies in children and adult cancer patients treated with chemotherapy have shown that chemotherapeutic agents can impact their cognitive functioning.[3-5] The phenomenon of "chemo-brain" has been described as an array of long-term disturbances in cognitive functioning. Patients experience deficiencies in attention, concentration, memory, information processing, judgment and planning. These cognitive abilities are clustered as executive functioning (EF).

Imaging studies attempted to uncover the neural substrate of difficulties in executive functioning after chemotherapy in adults.[6] An association between adjuvant chemotherapy and white matter microstructure has been found in a longitudinal study in young women treated for breast cancer. The chemotherapy-treated group performed worse on a detailed cognitive assessment and had an affected white matter microstructure in frontal, parietal and occipital brain regions.[7,8] Also in children there is evidence that chemotherapy can result in alterations in the brain and difficulties in EF.[9] However, the pathophysiological basis of chemotherapy-induced executive dysfunction in adults and children remains inconclusive.[10]

The development of the central nervous system continues throughout pregnancy and after birth and therefore prenatal exposure to chemotherapy could have a potential effect on EF at a later stage of the development. Data on these potential effects are scarce and only a few studies reported on cognitive outcome and executive functions of children exposed to antenatal chemotherapy.[11,12] Amant et al. reported on 96 children (median age, 22 months: range, 12 to 42 months) exposed to antenatal chemotherapy.[13] All children underwent a neuropsychological assessment and the results were compared to those of a control group, matched for gestational age at birth, country of origin and edition of the test that was used. The results were reassuring since no significant differences in cognitive outcome were found at this early stage of development. However, the median follow-up period was only 22 months, too short to reliably delineate the long-term safety on cognitive development. In addition, frontal brain regions responsible for EF develop during childhood and EF may become more demanding at school-age. Therefore, long-term

follow-up of these children is considered highly important. This study aims to investigate EF of 6 year old children prenatally exposed to chemotherapy.

METHODS

Study participants

This international cohort study is based on a collaboration between national referral centers in Belgium and the Netherlands, both members of the International Network on Cancer, Infertility and Pregnancy (INCIP). Children born to women diagnosed with cancer during pregnancy (with or without treatment during pregnancy) (study group) were invited to participate in follow-up. The outcomes of the study group were compared to the results of children born from healthy women after an uncomplicated pregnancy and preterm born children without signs of infection or neonatal complications (control group). Children were identified and enrolled prospectively (during pregnancy) or retrospectively (between birth and 6 years) and all children were prospectively examined at the national referral centers. All women treated with chemotherapy during pregnancy and their children, referred to one of the participating centers in Belgium and the Netherlands, were invited to take part in the study. In the study group all children received chemotherapy after the first trimester of pregnancy, alone or in combination with radiotherapy and / or surgery. Preterm born control children were recruited through the screening of birth lists from the participating centers. Control children born full term were recruited by distributing information letters in nurseries and by advertising on the webpage of the hospital. The study and control children were 1:1 matched with respect to country, gender, age, gestational age at birth and language of the tests. There were no exclusion criteria for study children. Exclusion criteria for control children were based on all pregnancy-related maternal problems (e.g. hypertension, preeclampsia, gestational diabetes with medical treatment, liver problems, epilepsia) or neonatal problems (e.g. asphyxia, admission to neonatal ward because of infections, long-term need of oxygen, malformations, brain lesions) that impact on cognitive development. The research protocol was approved by each institution and written parental informed consent was provided for each child. The study is registered as ClinicalTrials.gov, NCT00330447.

Study testing and outcomes

We collected oncological, obstetrical and neonatal data for each mother-child pair. At the predefined age of 6 years, parents of study and control children filled out the French or Dutch version of the Behavior Rating Inventory of Executive Function (BRIEF) questionnaire on EF and a questionnaire on general health problems. Intelligence was

examined using the Wechsler Preschool and Primary Scale of Intelligence – third edition (WPPSI-III).[14,15]

The BRIEF Parent form contains 75 items that assess eight clinical scales of executive functioning: inhibit, shift, emotional control, initiate, working memory, plan/organize, organization of materials and task monitor. Three index scores were derived from these clinical scales: Behavioral Regulation Index (BRI), Metacognition Index (MI), and Global Executive Composite (GEC). Language, age and sex-specific norms were used to convert raw scores to T-scores. The BRIEF has demonstrated good retest reliability: French version (parent, r = .76 < > .88) and Dutch version (parent, r = .61 < > .95).[16,17] The BRIEF is useful for evaluating children with a variety of executive problems.[16-19]

Statistical analysis

Descriptive statistics were used to describe maternal oncologic data, demographic characteristics of both groups, results of the health questionnaire and results of the intelligence test.

We converted raw scores into standardizes scores for the intelligence test and the BRIEF questionnaire, according to normative data for the country. The Mann-Whitney U test was used to investigate between-group differences for continuous variables and the chi-square or Fisher's exact test for categorical data. Preliminary assumptions testing indicated that Intelligence Quotient (IQ) scales were normally distributed, therefore independent-T-test was used to compare IQ scores. The Spearman's rank-correlation coefficient was used to investigate the association between death of the mother and informant of the BRIEF and to investigate the association between the outcome scales of the BRIEF and between-group differences. All analyses were conducted using IBM SPSS Statistics 25. A P value of less than 0.05 was considered to indicate statistical significance for all analyses.

RESULTS

Characteristics of the study children and the mothers

This interim analysis was performed with a data cutoff at February 6, 2019. Figure 1 shows the study design and recruitment. In total, 37 children born to 34 mothers (3 women carrying twins) treated with chemotherapy during pregnancy were included, of whom 29 from Belgium and 8 from the Netherlands. Breast cancer was diagnosed in 26 mothers (76.5%), cervical cancer in 3 mothers (8.8%), tongue cancer in 2 mothers (5.9%), gastric cancer in 1 mother (2.9%), Hodgkin lymphoma in 1 mother (2.9%) and non-Hodgkin lymphoma in 1 mother (2.9%). During pregnancy, 11 children (29.7%) were exposed to chemotherapy alone, 22 children (59.5%) were exposed to chemotherapy and surgery and 4 children (10.8%) were exposed to chemotherapy, surgery and radiotherapy.

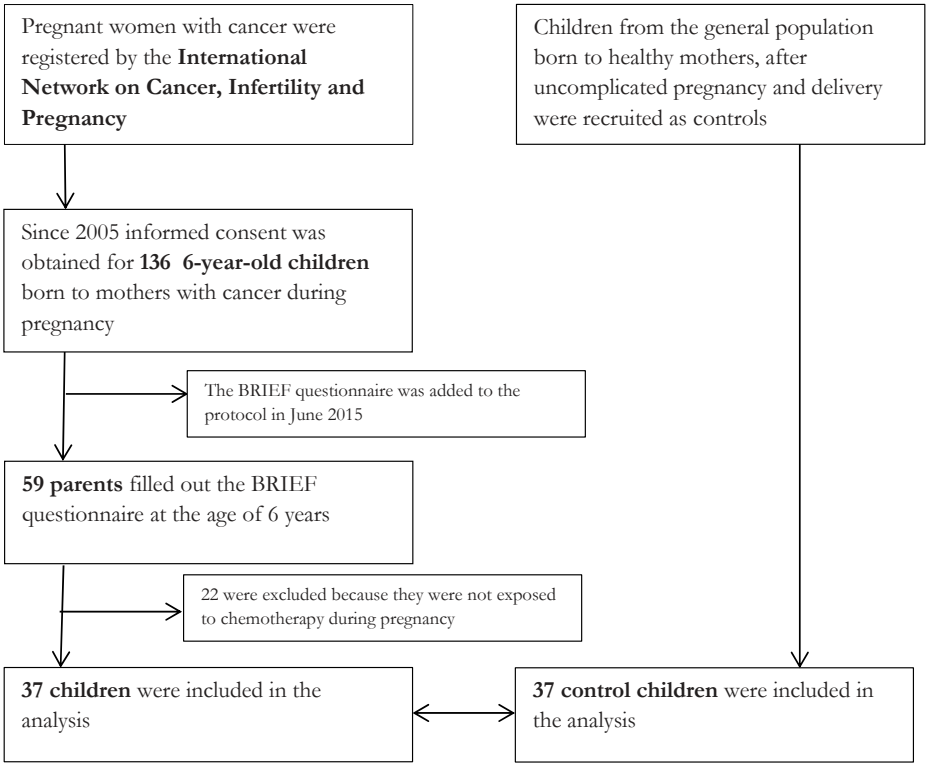

Figure 1: Study design and recruitment
This follow-up study was started in 2005. The BRIEF questionnaire was added to the protocol in June 2015. The neurologic and cardiac outcomes of 37 children 6-year-old children were previously analysed.[27] Study children and control children were matched to age, gestational age, gender, country of origin and edition of the intelligence test that was used.

Eight children (21.6%) lost their mother before they were 6 years old. Median follow-up time between death of the mother and date of examination was 50 months.

Characteristics of the study and control group

Outcomes of general health, the intelligence test and the BRIEF Parent form were obtained for 37 study children and 37 matched controls. In total, 74 children participated, of whom 42 females (56.8%) and 32 males (43.2%). Median age at date of examination was 6.1 years in the study group and 6.2 years in the control group (range both groups: 5.3 – 7.0). In the cancer in pregnancy group, median gestational age at birth was 35.6 weeks (range 31.1-38.5). In the control group, median gestational age at birth was 35.5 weeks (range 30.4-39.5).

Children from the study and control group were compared for several background variables. There were no statistically significant differences in age, gestational age at birth, country, gender, education level of parents and language of the test between the two groups (Table 1 and 2).

Table 1: Demographic characteristics of the children

Characteristic	**Cancer in pregnancy group (N = 37)**	**Control group (N = 37)**	**P Value**
Median age (range) - years	6.1 (5.3-7.0)	6.2 (5.3-7.0)	
Median gestational age (range) - weeks	35.6 (31.1-38.5)	35.5 (30.4-39.5)	
Country – number (%)			
Belgium	28 (75.7%)	28 (75.7%)	
the Netherlands	9 (24.3%)	9 (24.3%)	
Sex – number (%)			
Male	16 (43.2%)	16 (43.2%)	
Female	21 (56.8%)	21 (56.8%)	
Highest level of education of parents – number (%) *			
Mother			0.581
Primary school	0 (0%)	0 (0%)	
Secondary school	15 (40.5%)	13 (35.1%)	
Bachelor	11 (29.7%)	11 (29.7%)	
Master's degree or higher	11 (29.7%)	13 (35.1%)	
Father			0.440
Primary school	0 (0%)	2 (5.4%)	
Secondary school	14 (37.8%)	15 (40.5%)	
Bachelor's degree	11 (29.7%)	9 (24.3%)	
Master's degree or higher	12 (32.4%)	11 (29.7%)	
Death of mother	8 (21.6%)	0 (0%)	<0.01
Scores on the intelligence scale º			
Full Scale IQ	104.1 (99.4 – 108.7)	108.7 (105.0 – 112.5)	0.119
Verbal IQ	103.6 (99.0 – 108.3)	110.5 (107.3 – 113.8)	0.016
Performance IQ	104.5 (100.3 – 108.8)	105.5 (100.2 – 110.9)	0.767
Processing Speed	97.9 (93.1 – 102.8)	102.4 (97.0 – 107.8)	0.219

*Levels of education according to the European education system.
ºThe mean and 95% CI of the Intelligence scales.

Table 2: Patient characteristics of the BRIEF questionnaire

	Cancer in pregnancy group (N = 37)	**Control group (N = 37)**	**P Value**
Informant of the BRIEF Questionnaire			0.043
Mother	26 (70.3%)	33 (89.2%)	
Father	11 (29.7%)	4 (10.8%)	
Language of the test – number (%)			
Dutch (Flemish norms) §	18 (48.6%)	18 (48.6%)	
French	10 (27.0%)	10 (27.0%)	
Dutch	9 (24.3%)	9 (24.3%)	

§The manual of the Dutch version of the BRIEF includes Dutch and Flemish norms.

General health

In two children in the study group congenital malformations were reported, one child was born with an absent uvula and inguinal hernia and the other child with naevus flammeus in the groin. In the control group one child was born with polydactyly. The incidence of different types of medical problems, the need for surgery, supportive psychosocial and (para)medical care as reported by the parents with the general health questionnaire were comparable between the study and control group (Table S1).

Intelligence

Full Scale IQ was comparable between the study and control group (M = 104.1, 95% CI 99.4 to 108.7 versus M = 108.7, 95% CI 105.0 to 112.5) (p = .119). There were no significant between-group differences in Performance IQ or Processing Speed (M = 104.5, 95% CI 100.3 to 108.8 versus M = 105.5, 95% CI 100.2 to 110.9 and M = 97.9, 95% CI 93.1 to 102.8 versus M = 102.4, 95% CI 97.0 to 107.8) (p = .767 and p = .219). However, Verbal IQ was significantly lower in the study group (M = 103.6, 95% CI 99.0 to 108.3 versus M = 110.5, 95% CI 107.3 to 113.8). Since there was substantially more variance in the verbal IQ scores of the study group, Welch's t-test was used to compare the study group and the control group. The t test was significant, $t(64.1) = -2.5$, p = .016, two-tailed, 95% CI -12.5 to -1.3 (Table 1).

BRIEF outcomes

Mothers in the control group were more likely to fill out the BRIEF. In the study group, 26 mothers and 11 fathers filled out the questionnaire versus 33 mothers and 4 fathers in the control group (p = .043) (Table 2). Informant was related to death of the mother (R_s = -0.690, p < .01). In the cases of maternal death, fathers filled out the questionnaire. In the study group informant was related to emotional control (R_s = -0.377, p = .021). Fathers from the study group (11 children) reported on average 11 points lower emotional

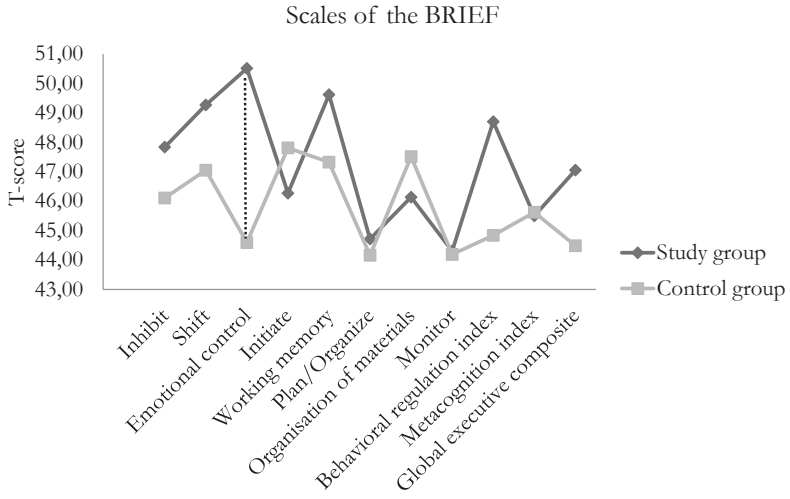

Figure 2: Profile of the BRIEF outcomes scales
The dotted line represents the significant difference in emotional control between the two groups, $p < .05$.

control score compared to mother's report (26 children). In further analyses, informant was included as a covariate, because of the difference between the two groups and the possible difference of assessing EF by mother or by father.

The primary scales of the BRIEF: BRI, MI and GEC revealed no between-group differences (Fig. 2). With regard to the clinical scales of EF: inhibit, shift, initiate, working memory, plan/organize, organization of materials, task monitor (seven out of eight) revealed no between-group differences. However, the score on the emotional control scale was significantly higher in the study group (Median T-score = 48) compared to the control group (Median T-score = 43) (U = 492.5, z = -2.1, p = .037) (Fig. 2). In total, 7 parents (18.9%) from the study group reported a clinical T-score (T-score > 65) compared to 2 parents (5.4%) from the control group. In both groups verbal IQ was not related to emotional control (study group R_s = -0.015, p = .931 vs. control group R_s = -0.157, p = .352). There were no gender differences in emotional control scores. After accounting for the informant of the test, emotional control was significantly higher in the study group F (1,71) = 4.78, p = 0.032.

DISCUSSION

Children prenatally exposed to chemotherapy do not differ in the development of executive functions compared to their matched controls. In this study, we noted adequate EF in both groups of the cohort of 6 year old children as reported by the BRIEF questionnaire

which was filled out by parents. However, a difference in emotional control was found. Parents of children prenatally exposed to chemotherapy reported more difficulties related to emotional control of their children than parents of children in the control group. A higher emotional control means that children have more difficulties with effectively managing and responding to an emotional experience. In terms of behavior, children may have more often explosive tantrums, hysterical laughter, are more impulsive and have a lower frustration tolerance.[16] Although the scores were overall within normal ranges, the results indicate that children from the study group have more difficulties to modulate emotions and behavior than children from the control group.

Cancer during pregnancy is a challenging life event that may cause prenatal maternal stress. In a study of Loomans et al. long-term outcomes of children exposed to antenatal maternal state-anxiety were evaluated.[20] Children exposed to antenatal maternal anxiety reported more overall problems in behavior, emotional symptoms, peer relationship problems, conduct problems and less prosocial behavior at age five. Different mechanisms have been described to explain the effect of prenatal maternal stress on the development of the child. First, increased glucocorticoids because of maternal stress may cross the placenta and thereby also increase the stress hormone level of the fetus.[21] A second hypothesis described the phenomenon of blood flow, because of the fact that maternal emotional and physical stress and anxiety may increase the release of noradrenaline and adrenaline. These increased levels can result in impaired uterine artery blood flow and thereby oxygen restriction and direct stress for the fetus.[22] Last, maternal stress hormones can have an impact on the development of the Hypothalamic-Pituitary-Adrenal axis and brain regions such as the prefrontal cortex and limbic system of the fetus[23]. In addition, these regions are responsible for EF and emotional regulation. It is therefore possible that the increased number of problems with emotional regulation in children prenatally exposed to maternal cancer and chemotherapy may be related to antenatal maternal stress.

Another contributing factor might be prenatal and postnatal bonding, which might be at risk in case of cancer during pregnancy. Parents have to deal with the cancer, uncertainly, feelings of guilt, questions and anxieties, which could affect the interaction with the child and lead to emotional difficulties in the mother-child relationship.[24,25] A recent study of Betchen et al. in mothers diagnosed with cancer during pregnancy showed that maternal stress is associated with poorer verbal performance and infant emotional states.[25] In addition, attachment is associated with predicting verbal comprehension and cognitive abilities in children.[26] Interestingly, the children from the study group had also significantly lower verbal intelligence scores compared to the controls. In our study, we hypothesized that children growing up after the death of their mother could be more at risk for emotional regulation problems. In the cases of maternal death, fathers filled out the questionnaire and reported overall lower emotional control T-scores, indicating less emotional regulation problems, which is not concordant with what was expected.

However the group was small and therefore we believe we have to interpret this finding with caution.

Our study has some limitations. This study only analyzed a relatively small group of patients. In addition, the development of EF may be influenced by genetic variation and environmental influences. Hence, it is possible that the child's EF is influenced by other factors than prenatal exposure to maternal malignancy and chemotherapy. In this study, we tried to correct for these confounding factors by including a matched control group and evaluating general health status and intelligence. Another limitation to consider is that EF gradually develop and require more complex functioning later in life, therefore 6 years of follow-up is maybe too short to document long-term effects in EF.

Despite our small sample, our data suggest that children prenatally exposed to chemotherapy do not differ in the development of executive functions compared to their matched controls at 6 years. The results are reassuring since all scores were within normal ranges. This is consistent with previous studies in which general health status and cognitive functions were evaluated in children prenatally exposed to chemotherapy.[12,13] However the difference in emotional control between the two groups underscores the need of long-term follow-up of these children, and the need for validation in larger cohorts. In addition, this study suggests that during follow-up for these children, surveillance of emotional development is important. Early screening of emotional development may prevent difficulties in emotion regulation.

SUPPLEMENTARY APPENDIX

Table S1: Overview of the general health questionnaire

	Cancer in pregnancy group (N = 37)	**Control group (N = 37)**	**P value**
Respiratory disease	3	6	.286
Eye diseases	5	4	.722
Ear disorders	1	1	.948
Heart and cardiovascular diseases	0	0	*
Gastrointestinal disorders	2	0	.152
Diseases of bones and joints	1	0	.314
Kidney and urinary system disorder	4	2	.394
Hormone disorder	0	0	*
Skin or hair disorders	3	5	.454
Dental problems	2	3	.643
Allergies	5	5	*
Diseases of the genital tract	2	1	.556
Congenital disorders	2	1	.556
Hereditary disorders	1	0	.314
Serious health problems	0	0	*
Skeletal muscle disorders	2	2	*
Neurological disorders	1	1	*
Other problems	3	3	*
Surgery	9	10	.790
Supportive care	3	2	.643

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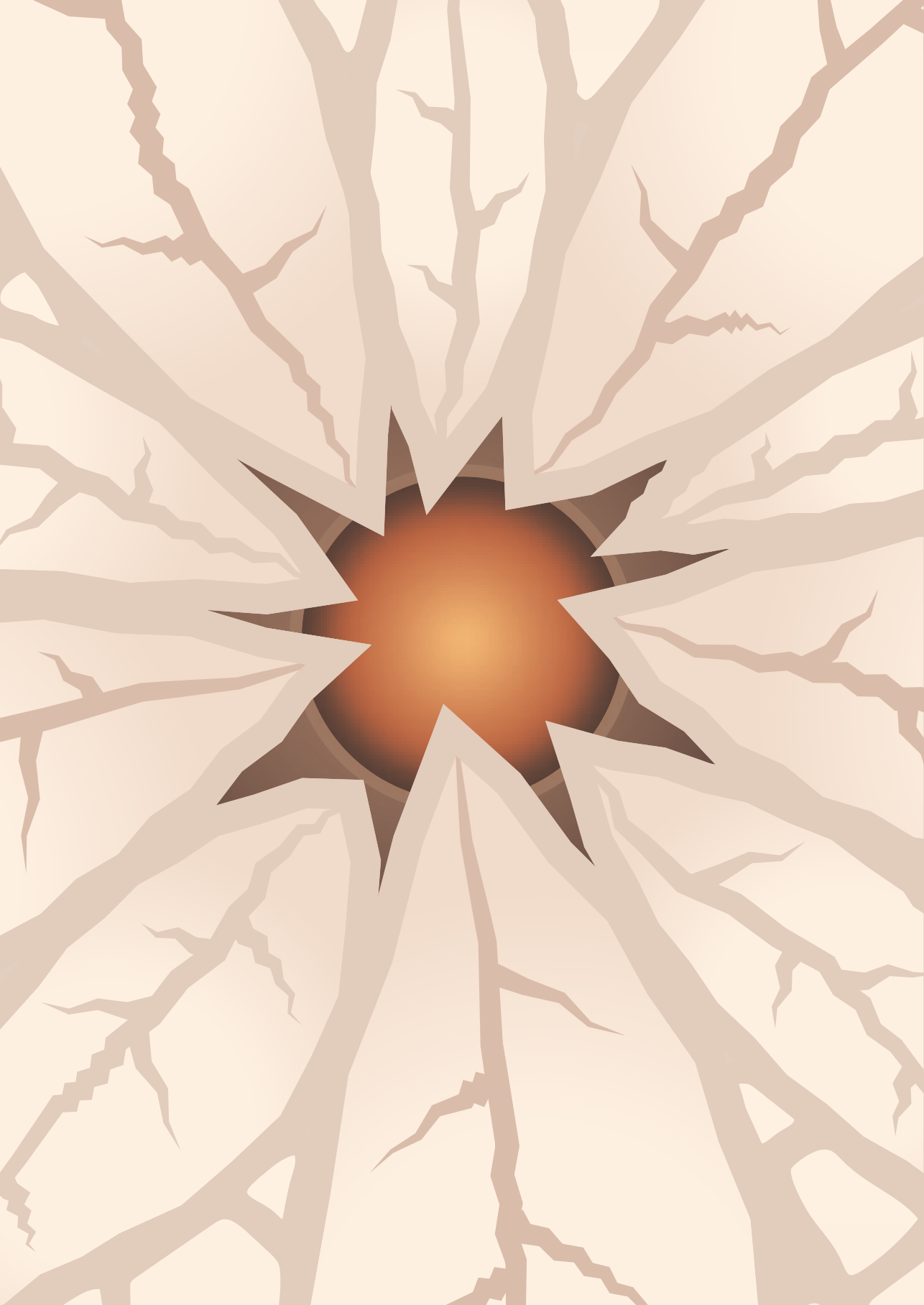

Chapter 5.

Long-term neurodevelopmental outcome after prenatal exposure to maternal hematological malignancies with or without cytotoxic treatment

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ABSTRACT

Data on the long-term neurodevelopmental outcomes of children exposed to hematological maternal cancer with or without treatment during pregnancy are lacking. A total of 57 children, of whom 33 males and 24 females, prenatally exposed to hematological malignancies and its treatment, were invited for neuropsychological and physical examination at 18 months, 36 months, 6, 9, 12, 15 and 18 years of age. Oncological, obstetrical, neonatal and follow-up data of these children were collected. Parents were asked to complete questionnaires on their child's general health, school performances, social situation, behavioral development, executive functioning and if their child receives supportive care. Non-Hodgkin lymphoma was diagnosed in 35.1%, Hodgkin lymphoma in 28.1%, acute myeloid leukemia in 15.8%, chronic myeloid leukemia in 12.3% and acute lymphoblastic leukemia in 8.8 %. Cognitive development at a median age of 10.7 years was within a normal range. In subgroup analyses of children in early childhood, the gestational age at birth was correlated with the cognitive outcome at a median age of 1.7 years. Scores for language development, intelligence, attention, memory and behavior, as well as clinical neurological and general pediatric examinations were within normal ranges. In subgroup analyses, the needs of supportive care in the child was associated with the loss of the mother. Prenatal exposure to hematological maternal malignancies with or without treatment did not affect the neurodevelopment of the child in the long-term. Yet, caution is indicated and surveillance of emotional development of the child is needed especially when the mother deceased to cancer.

INTRODUCTION

Cancer is diagnosed during 1 in 1000 pregnancies with a cancer type distribution that is similar to non-pregnant women. After breast cancer, thyroid cancer and skin cancer (including melanoma), lymphoma is the fourth most common cancer type diagnosed during pregnancy, with an estimated prevalence of 1 in 6000 pregnancies.[1,2] In contrast, leukemia during pregnancy is very rare, 1 in 75000 to 100000 pregnancies.[2] Typical symptoms of hematological malignancies can be falsely attributed to pregnancy such as fatigue, nausea and abdominal pain, leading to a delay in diagnosis. A maternal malignancy, most frequently hematological malignancies, can also be detected by a discordant result of the non-invasive prenatal testing (NIPT).[3] The use of NIPT is increasing likely to result in more cancer in pregnancy diagnoses.

Chemotherapy from the second trimester onwards is considered to be relatively safe since no more or other congenital malformations are found after chemotherapy compared to the normal population. Increasing awareness of the feasibility of antenatal chemotherapy resulted in more pregnant patients receiving treatment over the past years.[4] The general health, the neurocognitive and cardiac outcome of children prenatally exposed to maternal cancer in age ranges of 18 months until 18 years were previously published by the International Network of Cancer, Infertility and Pregnancy (INCIP).[5-7] Cognitive and cardiac outcomes were within normal ranges, but subtle differences in development were found. In early childhood, preterm birth was a predictor of worse neurodevelopmental outcome, however this association was independent of cancer treatment during pregnancy.[6] This study resulted in the recommendation to aim for a term delivery (after 37 weeks of gestation) and currently the overall frequency of preterm births in pregnancies complicated by cancer is decreasing. At 6-years, children prenatally exposed to maternal malignancy were at risk for lower verbal intelligence and visuospatial long-term memory scores and higher diastolic blood pressure.[7] In addition, verbal intelligence was more affected in children whose mother died than those with surviving mothers.

In 2020 a comprehensive literature review on long-term neurodevelopmental outcome was published.[8] Based on 17 cohort studies, no major cognitive abnormalities were reported, however it was concluded that more thorough follow-up of the children is required. In addition, results from most of these studies made no distinction in type of malignancy and the associated therapy. Hence, the study heterogeneity may mask significant differences in smaller subgroups and underscores the need for further research to identify whether specific subgroups of children born to women with a cancer diagnosis during pregnancy are at higher risk of developmental problems. Important in these subgroups is defining the specific impact of type of malignancy on child development. In addition, the first 1000 days after conception are a crucial period when the foundations of neurodevelopment are established.[9] Hematological malignancies and comorbidities such as stress, attachment

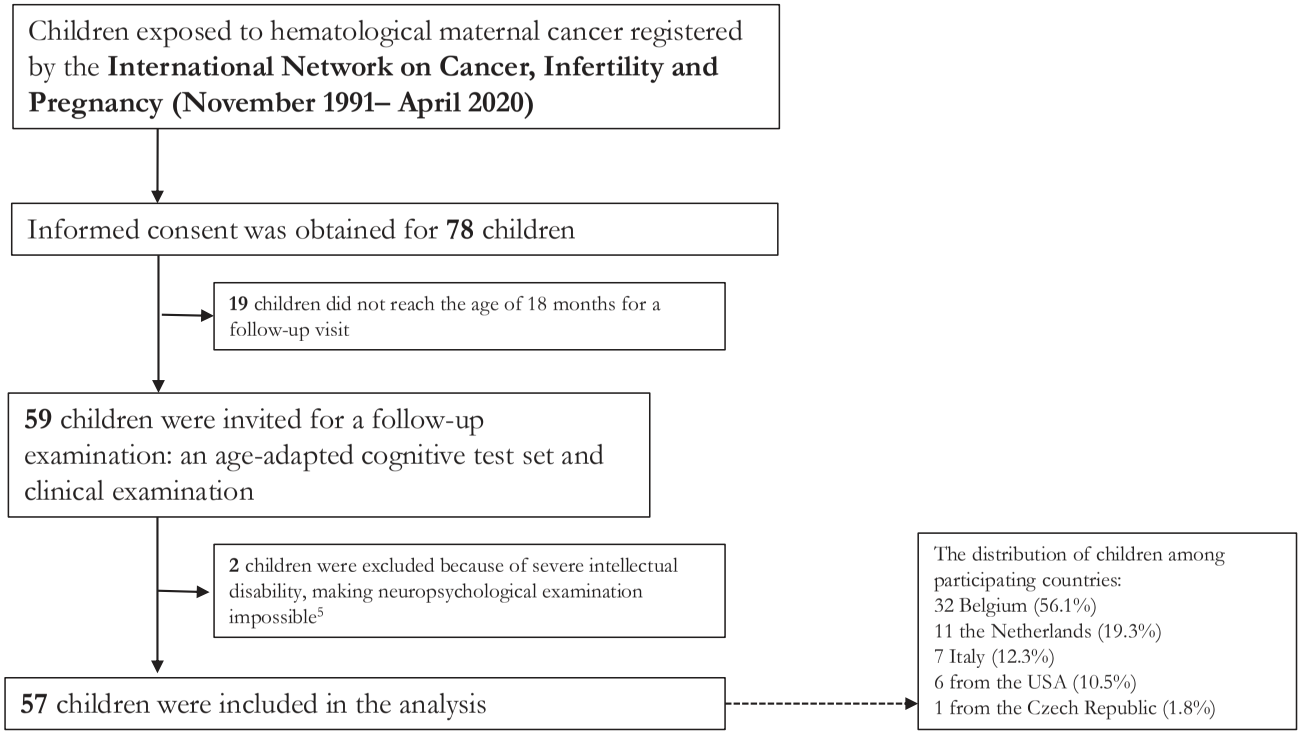

Figure 1: Study design and recruitment

issues, and malnutrition can weaken these foundations. Unfortunately, to date there is still a lack of knowledge about how the diagnosis and treatment in pregnancy may affect the neurodevelopment in the offspring.

Therefore, this study aims to describe the specific impact of maternal hematological malignancy and its treatment during pregnancy on the perinatal outcome, health status and neurocognitive development of the offspring.

MATERIALS AND METHODS

Study design and participants

This is a multicenter prospective cohort study, with data obtained from the long-term follow-up study of INCIP. Data were obtained from 7 referral centers in 5 countries (Belgium, Czech Republic, Italy, the Netherlands and the United States). Figure 1 summarized the study design and recruitment. Two children with a severe neurodevelopmental delay, which made it impossible to perform the neuropsychological examination, were excluded and previously published.[5] The ethical committee of each participating institution approved the study and written (parental) informed consent was obtained for each child. The full study protocol is available at www.cancerinpregnancy.org/study-protocols and the study is registered at ClinicalTrials.gov, NCT00330447.

Data collection and instruments

For each mother-child pair oncological, obstetrical and neonatal data were collected from the INCIP database, that contains data of patients diagnosed with any pregnancy-associated malignancy. Furthermore, the children were invited for neuropsychological and physical examination on predefined ages of 18 months, 36 months, 6, 9, 12, 15 and 18 years. Neuropsychological examination consisted of an age-adapted cognitive test set. For the purpose of the present study we focused on developmental indexes, intelligence, attention, verbal and non-verbal memory. During each visit, children underwent a clinical neurological and general pediatric examination and the parents were asked to fill out questionnaires on general health status, executive functioning and behavior of their child. An overview of the age-adapted tests is provided in Table 1.

Cognitive development

Cognitive development was tested at 18 months and 36 months using the Bayley Scales of Infant and Toddler Development III (BSID- III).[10,11] At 36 months, the language scale of the BSID-III was also obtained. From the age of 6 years onwards, intelligence was tested using the Wechsler Preschool and Primary Scale of Intelligence Revised or III (WPPSI-R or WPPSI-III[12,13]), the Wechsler Intelligence Scale for Children (WISC-III, WISC-IV

and WISC-V[14-16]), or the Wechsler Adult Intelligence Scale III or IV (WAIS-III or WAIS-IV[17,18]). The scores of these tests were referred to developmental index scores (at 18 months and 36 months) or Intelligence Quotient (IQ) (from 6 years of age). Different intelligence tests were used as this is a multicenter internal study and the currently used edition or revision of the Wechsler test was not always the same in all participating countries during the inclusion period.

Table 1: An overview of the age-adapted test sets

Cognitive development	**Cognitive assessment**	**Age**
Cognition	BSID-II or BSID-III	1–42 months
Intelligence	WPPSI-R or WPPSI-III or WPPSI-IV	6 years
	WISC-III or WISC-IV	9, 12 and 15 years
	WAIS-III or WAIS-IV	18 years
Attention: Alertness, Response inhibition, Divided attention, Selective attention and Attention control and flexibility	ANT	6, 9,12,15 and 18 years
Non-verbal memory	CMS	6, 9, 12 and 15 years
Verbal memory	AVLT	9, 12, 15 and 18 years
Behaviour checklist, questionnaire completed by the parents	CBCL	6, 9, 12 and 15 years
Executive function Behaviour, questionnaire completed by the parents	BRIEF-P	36 months
	BRIEF	6, 9,12,15 and 18 years
General health	**Assessment**	**Age**
Congenital anomalies	Clinical neonatal exam	0-1 months
Neurological assessment	Clinical neurological and general pediatric exam	1–42 months 6, 9,12,15 and 18 years
General health	Questionnaire	1–42 months 6, 9,12,15 and 18 years

The Bayley Scales of Infant Development – Second or Third edition (BSID-II, BSID-III)[11,35]. the Wechsler Preschool and Primary Scale of Intelligence – revised or third edition (WPSSI-R or WPPSI-III)[12,13], the Wechsler Intelligence Scale for Children – third, fourth or fifth edition (WISC-III, WISC-IV, WISC-V)[15,16,36], the Wechsler Adult Intelligence Scale – third or fourth edition (WAIS-III, WAIS-IV)[12,18], the Amsterdam Neuropsychological Tasks (ANT)[19], the Children's Memory Scale (CMS)[21], the Auditory Verbal Learning Test (AVLT)[20], the Behavior Rating Inventory of Executive Function (BRIEF)[25] and the preschool version (BRIEF-P)[24] and the Child Behavior Checklist (CBCL)[23].

Attention

Five subtasks from the Amsterdam Neuropsychological Tasks (ANT[19]) were used to evaluate different aspects of attention. ANT is a computerized program which enables to measure not only the accuracy of responses but also the reaction times. We used data

obtained from the subtasks: 'Baseline Speed', 'GoNoGo', 'Memory Search Objects 2 keys', 'Focused Attention Objects 2 keys' and 'Shifting Attentional Set Visual'.

Verbal and non-verbal memory

To evaluate learning and memory function for verbal material, and to track changes in memory function over time, the Auditory Verbal Learning Test (AVLT[20]) was used.

The Children's Memory Scale (CMS[21]) includes a series of tasks on verbal and non-verbal memory. CMS Numbers was used to evaluate verbal memory span and working memory. CMS Pictures assessed the memory span for visuospatial material. Learning and memory of non-verbal visuospatial material was assessed using CMS Dots.

Questionnaires on general health, behavior and executive functioning

Parents were asked to fill out a questionnaire which addressed general information such as their child's general health, school performance (at school ages), receiving supportive care, non-academic interests, social situation and important life-events. This questionnaire also addressed child's growth and any developmental or medical problems.[22] Furthermore, parents were asked to fill out a questionnaire on the incidence of internalizing and externalizing behavior problems (Child Behavior Checklist, CBCL[23]). Higher scores indicate more behavior problems.

To assess executive functioning, parents have filled out the preschool version (BRIEF-P[24]), or the Behavior Rating Inventory of Executive Function (BRIEF[25]). As outcome variables we used the Inhibitory-Selfcontrol Index, the Flexibility scale, the Emergent-Metacognition Index and the Global Executive Composite for the BRIEF-P. Outcome variables for the BRIEF were Behavioral-Regulation Index, Metacognition Index, and the Global Executive Composite.

Data management and analyses

Descriptive statistics were used to review maternal oncological data, demographic characteristics of the mothers and children, results of the health questionnaire, and clinical neurologic evaluations. For all children, raw scores of the neuropsychological tests were converted to standardized scores using normative data for the specific age-group provided by the manual of the respective test. We used the last available neuropsychological assessment for each child. Descriptive statistics were used to describe the outcome of the neuropsychological assessment. The relationship between cognitive outcome and gestational age was investigated using Pearson correlations. A Pearson's chi-square test of contingencies (with $\alpha = 0.05$) was used to evaluate whether dead of mother is related to receiving supportive care. For data analyses and reporting a Statistical Package for Social Sciences Version 25.0 (SPSS 25.0) was used.

RESULTS

Characteristics of the study children and the mothers

This interim analysis was performed with a data cutoff at April, 2020. In total, 57 children (born 1991-2017) were eligible for analysis of which 33 male (57.9%) and 24 female (42.1%). Thirty-eight children (66.7%) were exposed to chemotherapy in utero, 4 children (7.0%) were exposed to targeted therapy, 3 children (5.3%) were exposed to radiotherapy (with or without surgery), ten children (17.5%) were not exposed to any treatment, and of 2 children (3.5%) data on oncological treatment during pregnancy were missing. Non-Hodgkin lymphoma was diagnosed in 20 mothers (35.1%), Hodgkin lymphoma in 16 mothers (28.1%), acute myeloid leukemia in 9 mothers (15.8%), chronic myeloid leukemia in 7 mothers (12.3%) and acute lymphoblastic leukemia in 5 mothers (8.8%). Additional information about the (timing of) diagnosis and specific treatments is provided in Table S1.

Perinatal outcome

The median gestational age at delivery was 36.4 weeks (range: 26.4 – 41.3) and the median birth weight was 2590 g (range: 720 – 4423). Sub-categories of preterm birth based on gestational age are provided in Table 2. Twenty-one children born preterm and 2 born full term (40.4%) were admitted in the neonatal intensive care unit. Six children (10.5%; median gestational age 33.8 weeks) were born with congenital malformations, wherefrom 1 child had contractures of limbs, 1 child had congenital laryngomalacia, 2 children had plagiocephaly, and 2 children had partial syndactyly (Table S2).

Table 2: Classification of delivery according to gestational age

	N = 57	%
Extremely preterm: <28 weeks	1	1.8%
Very preterm: 28.0 to 31.6 weeks	5	8.8%
Moderately preterm: 32.0 to 33.6 weeks	5	8.8%
Late preterm: 34.0 to 36.6 weeks	19	33.3%
Full term: >/=37 weeks	27	40.4%

General health

Clinical neurological examination (n=40) did not show any focal neurological abnormalities, however two children had a delay in motor development (gestational age of 34.1 and 38.6 weeks).

Data from a health questionnaire addressing different types of medical problems reported by parents was available for 44 children (response rate; 57 %) (Table 3). One child used the drug risperidone for explosive and aggressive behavior. No other children used psychotropic medication.

Table 3: Overview of the different types of medical problems

	N	%
Respiratory diseases (asthma, RSV infection)	12	21.1
Eye condition (astigmatism, hypermetropia)	6	10.5
Glasses	7	12.3
Recurrent otitis	3	5.3
Patent ductus arteriosus	1	1.8
Gastrointestinal diseases (short bowel syndrome, constipation)	2	3.5
Kidney stones	1	1.8
Eczema	1	1.8
Recurrent dental cavities	2	3.5
Allergies	7	12.3
Diparesis	1	1.8
Epilepsia	1	1.8

Abbreviations: RSV = respiratory syncytial virus

Fourteen (24.6%) children needed a surgery in their lives (Table S3). Five children (8.8%) received supportive psychosocial care: 2 children (3.5%) received support for social-emotional development, 2 children (3.5%) received support at school because of hypersensitivity and dyslexia, and 1 child (1.8%) received support for performance anxiety. Learning disabilities, as reported by parents on this questionnaire, were reported in 8 children (14%) (Table 4).

Table 4: Overview of reported cognitive problems and learning disabilities in 8 patients (median gestational age: 36.3 weeks)

	N = 8*
Concentration problems	2
Repeated grades	2
Behavior problems	1
Problems regarding planning and organizing	1
Dyslexia	3
Dyscalculia	1

*Some children had multiple problems or disabilities.

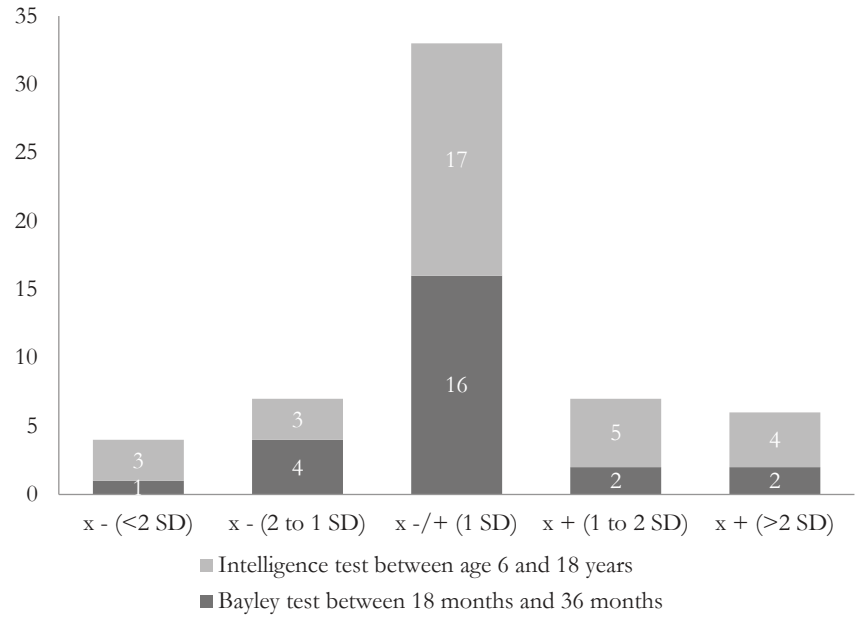

Figure 2: Distribution of the last performed Bayley or Wechsler intelligence test

Neurodevelopment

The median follow-up period at time of the last neuropsychological assessment of the children was 6.1 years (range: 1.4 – 18.8). Total scores for the children were within normal ranges, overall the median score was 100 (n=57; 95% CI = 96.9 – 104.6).

Figure 2 shows the distribution of the results for the last performed developmental or intelligence test (Bayley test [n=25, median assesment age of 1.70 years], Wechsler intelligence test [n=32; median assesment age of 10.7 years]). In early childhood the median score for the cognitive development scale assessed by the Bayley test was 95.0 (n=25; 95% CI = 93.4 – 104.3) and related to gestational age at birth (R_s = 0.459, P = 0.021). In the older age group the median score for total IQ of the Wechsler intelligence test was 101.5 (n=32; 95% CI = 96.6 – 107.8) and not related to gestational age at birth (R_s = 0.115, P = 0.531). We recorded normal language development at the age of 36 months and the secondary outcomes of the Wechsler tests at the age of 10 years were within normal ranges. In both groups, the scores were not related to the duration of chemotherapy exposure during pregnancy (R_s = 0.153, P = 0.410).

The results on the different subtasks of attention, verbal and non-verbal memory were within normal ranges. Table 4 and 5 in the supplementary appendix gives a detailed overview and distribution of the results on attention and memory. Median scores on internalizing problems, externalizing problems and the total amount of problems on the Child Behavior Checklist (1.5-5 years and 6-18 years) were for both groups within normal

ranges. Data from the BRIEF-P and BRIEF were also within the normal ranges for both groups.

Death of mother

Ten mothers (17.5%) died from their disease with a median time period of 1.4 years (range: 0.5 – 5.2) after diagnosis. The median age of the children at maternal decease was 1.4 years (0.4 – 13.3). From five children whose mother died, three children received supportive psychosocial care . The association between receiving supportive care and dead of the mother was considered as a medium sized effect, $\Phi = .31$, although the chi-square test was not statistically significant χ^2 (1, $N = 43$) = 4.69, p = 0.08.

DISCUSSION

In this multicenter prospective cohort study, neurodevelopment, perinatal outcome and general health was reported of 57 children born to mothers diagnosed with hematological malignancies during pregnancy. Although the incidence of preterm delivery in these children was high (52.7%), the cognitive development at a median age of 10.7 years was normal. In subgroup analyses, the cognitive development of 25 children at median age of 1.7 years was related to their gestational age at birth. This finding confirmed the negative prognostic effect of preterm birth on early cognitive development, which is highlighted in previous studies.[5,6] This relationship was no longer present in the older age group, which can be explained by the fact that mild developmental delay in premature children will caught-up with increasing age.[26]

In general, the outcomes for language development, intelligence, attention and memory were reassuring. All scores were within normal ranges. Developmental index scores and Full Scale intelligence scores were not related to the duration of chemotherapy exposure during pregnancy. Additionally, reassuring results were found for behavioral development. All scores were within normal ranges. Our results are in line with a previous study on children born to mothers with hematological malignancies suggesting that these children are not at risk for neurodevelopmental problems at a median follow-up of 18.7 years.[27] However in this study in-depth testing was lacking.

Maternal outcomes of pregnant women with non-Hodgkin and Hodgkin lymphoma has been recently studied. These studies showed comparable maternal survival between pregnant and non-pregnant patients.[28,29] In our cohort ten mothers died from their disease (17.5%). Death of the mother is a major life event that potentially influence child development. Previous studies showed an association between anxiety and stress during pregnancy with adverse birth outcomes (e.g. spontaneous abortion, preterm labor, growth restriction) and problems across several domains (cognitive, behavioral and emotional) in

the child.[30,31] In subgroup analyses, receiving supportive care was associated with the dead of the mother. Three children whose mother died received support for social-emotional problems as reported by the fathers. The need for supportive care in these children may be explained by the stress associated with the loss of their mothers. Paternal roles become different and fathers are often challenged to adjust to single parenthood while managing their own grief.[32] Earlier studies have highlighted that widowed fathers often experience depressive feelings and feel incompetent across several domains.[33,34] These families are at risk for high levels of distress and may explain the need for supportive care. Unfortunately, needs of widowed fathers have been overlooked in literature and publications often only concern single parenthood in fathers, because of separation or divorce. To the best of our knowledge, this is the first study that shows an association between maternal bereavement due to the cancer on the need for supportive care of the child. The complexity of managing hematological cancers in pregnancy highlight the need for a multidisciplinary approach in an experienced center where gynecologist, oncologist, pediatricians, neonatologist, nurses and psychologist can easily contribute. Further research of psychosocial effects in families confronted with cancer during pregnancy is needed, including more in-depth testing by standardized assessments of stress, emotional functioning and sensory processing to elucidate psychosocial risks of children born from mothers with a poor prognosis.

Our study has some limitations. The median follow-up period was 6.1 years and may have been too short to identify neurocognitive problems that become more apparent at later school-ages. In addition, our study group was small and postnatal environmental factors challenge the research on the long-term neurodevelopmental outcome of prenatal exposure to hematological cancers during pregnancy. Larger samples and follow-up until adult ages is needed to investigate the impact on cognitive functions and psychosocial development after maternal hematological cancer diagnosed during pregnancy.

In conclusion, our data did not detect major long-term neurodevelopmental problems in children prenatally exposed to hematological maternal malignancies. The reassuring data support the current policy to treat hematological cancer also during pregnancy. However, caution is indicated and surveillance of emotional development of the child is needed especially when the mother deceased to the cancer.

SUPPLEMENTARY APPENDIX

Table S1: Information about the diagnosis and specific treatments

Diagnosis	**Median**
Maternal age at the time of diagnosis	31 years (19.0 – 41.0)
Gestational age at diagnosis	21 weeks (5.1 – 35.3)

Trimester of diagnosis	**N**	**%**
Before pregnancy	2	3.6
First	4	7.0
Second	41	71.9
Third	7	12.3
Missing	3	5.2

Chemotherapy scheme in 38 women	**N**	**%**
ABVD	14	24.6
AIDA	2	3.5
AraC-Ida	1	1.8
CHOP	5	8.8
Daunorubicin/Cytarabine	2	3.5
HOVON 37 without L-asparaginase	1	1.8
HOVON 70	1	1.8
Induction/HAM	1	1.8
R-ACVBP	1	1.8
R-CHOP	9	15.8
Vincristin	1	1.8

Table S2: Congenital malformations were reported in 6 children

Cancer type	**Treatment during pregnancy**	**GA at delivery in weeks**	**Congenital anomalies (n=6, 10.5%)***
acute lymphoblastic leukemia	Chemotherapy: HOVON 37 without L-asparaginase	28 weeks	Contractures of limbs, Major, Q74.3
acute myeloid leukemia	No treatment	35 weeks	Plagiocephaly, Minor, Q67.3
acute myeloid leukemia	No treatment	32 weeks	Plagiocephaly, Minor, Q67.3
Hodgkin lymphoma	No treatment	29 weeks	Congenital laryngomalacia, Minor, Q31.5
Hodgkin lymphoma	Chemotherapy: ABVD	31 weeks	Syndactyly, Major, Q70
Hodgkin lymphoma	Chemotherapy: ABVD	36 weeks	Syndactyly , Major, Q70

*Classification according to EUROCAT

Table S3: Overview of the performed surgeries in 14 children

Surgeries	**N = 14***
Ear tube surgery	5
Tonsillectomy and/or adenoidectomy and/or polypectomy	8
Tear duct drainage	1
Lobectomy	1
Inguinal hernia closure	2
Umbilical hernia closure	1
Dental surgery	1
Other (fracture of arm, correction of lazy eye, correction of hymen imperforatus, correction of the outer ear, reconstructive surgery of skin because of burns)	4

*Some children needed multiple surgeries

Table S4: Overview of the attention outcomes

Measurement	No.	6 years				No.	9-18 years			
		Median	Median age	95% CI			Median	Median age	95% CI	
				Lower	Upper				Lower	Upper
Alertness										
RT of dominant and non-dominant hand	7	-0.03	6.10	-0.97	0.83	21	-0.29	12.10	-0.50	-0.63
Response inhibition										
RT hits	7	1.00	6.10	-0.40	1.73	12	0.00	9.23	-0.79	1.46
Number of false alarms	7	-1.00	6.10	-1.48	0.88	12	1.00	9.23	-0.46	2.63
Divided attention										
Effect of memory load on RT	7	0.12	6.10	-0.48	1.04	19	-0.31	12.09	-0.45	0.43
Effect of memory load on accuracy	7	0.15	6.10	-1.04	1.20	19	-0.10	12.09	-2.68	0.38
Selective attention										
Effect of distraction on RT	7	0.09	6.10	-0.94	0.60	20	0.13	12.09	-0.02	0.39
Effect of distraction on accuracy	7	-0.33	6.10	-0.51	1.32	20	-0.10	12.09	-0.53	0.96
Attention control and flexibility										
RT part 3	*	*	*	*	*	20	-0.40	12.13	-0.77	0.26
Total numbers of errors part 3	*	*	*	*	*	20	0.30	12.13	0.10	1.55

Higher median scores indicate worse performance.

The effect of memory load on reaction time is calculated as $((\text{RT hits + RT CR})_{part2} - (\text{RT hits + RT CR})_{part1})/2$ or $((\text{RT hits + RT CR})_{part3} - (\text{RT hits + RT CR})_{part1})/2$. Higher numbers indicate a larger effect of memory load on reaction time.

The effect of memory load on accuracy is calculated as $((\text{P-MI + P-FA})_{part2} - (\text{P-MI + P-FA})_{part1})/2$ or $((\text{P-MI + P-FA})_{part3} - (\text{P-MI + P-FA})_{part1})/2$. Higher numbers indicate a larger effect of memory load on accuracy. The effect of distraction on reaction time is calculated as RT CR [irrelevant target] – RT CR [non-target]. Higher numbers indicate a larger effect of distraction on reaction time. The effect of distraction on accuracy is calculated as P-FA[irrelevant target] – P-FA[non-target]. Higher numbers indicate a larger effect of distraction on accuracy.

Abbreviations: ANT = Amsterdam Neuropsychological Testing, RT = Response time

* This test was not performed in 6 years

Table S5: Overview of the memory outcomes

Tested	Median age	Median z score or median standard scores	95% CI	
			Lower	Upper
AVLT				
Learning of verbal material	12.20	0.53	-0.26	1.10
Short-term verbal memory	12.20	0.68	-0.15	1.08
Long-term verbal memory	12.20	0.59	-0.10	1.26
CMS Numbers				
Verbal memory span	12.07	9.00	7.80	9.91
Verbal working memory	12.07	9.00	8.40	10.53
CMS Dots				
Visuospatial short-term memory	12.04	12.0	10.48	12.01
Visuospatial long-term memory	12.04	12.0	9.99	12.15
CMS Pictures				
Visuospatial memory span	12.04	12.0	10.30	12.46

Abbreviations: AVLT =Auditory Verbal Learning Test, CMS = Children's Memory Scale
For CMS we used standardized scores (1-19)

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Chapter 6.

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 21 weeks 6 days (range 6 – 30). 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.[1] 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.[2] 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.[3]

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. The stage distribution of 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.[4] 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.[5] As a result, gastric cancer is often diagnosed in more advanced cancer stages. Localized gastric cancer (>T2) can be treated with curative intent by surgical resection and (peri- or post) operative chemotherapy.[6] 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 over-expressing 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.[7] 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.[7] 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.[7] 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.[3,8,9] However, biological behavior and response to treatment may show geographic differences.[10] 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 birth weight 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.

Ethical approval

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 (Supporting Information Table S1). 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.

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.

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* (Median (range))	21 weeks 6 days ($6^{5/7}$ – $30^{1/7}$)
Gestational age at delivery (Median (range))	32 weeks 3 days ($19^{2/7}$- $39^{2/7}$)
History of smoking	4 (31%)
Histopathology	
Diffuse type	12 (100%)
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)	3 (23%)
Deferral of treatment until after delivery	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	3 (23%)
Pre-eclampsia	1 (8%)
Spontaneous preterm delivery	4 (44%)
Low birth weight (<P10)**	2 (20%)
Mode of delivery	8 (80%)
Vaginal delivery	0
Cesarean section	
Placental metastasis	
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)

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 and 3 days 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 2.

Table 2: Pediatric outcome of four children prenatally exposed to chemotherapy for gastric cancer, included in the INCIP follow-up study

Case	Gestational age at diagnosis (weeks)	Gestational age at delivery (weeks)	Age at follow-up	Chemotherapy during pregnancy	General outcome	Cardiac outcome	Neurological outcome	Cognitive outcome	Supportive care
8	22	39	4 months	FOLFOX 6 cycles	Normal growth	No details	No details	No details	No supportive care
9	15	34	18 months	FOLFOX 7 cycles *Radiation exposure: 12mGy** Trastuzumab exposure during first trimester	Normal growth and development	No details	No neurological abnormalities	18 months: normal cognitive development for his premature age	No supportive care
11	6 (first trimester)	32	15 months	Carboplatin and paclitaxel 3 cycles	Normal growth and development	No abnormalities	Cerebral palsy left, epilepsy and hemianopia left-side	15 months: normal cognitive development for his premature age	0-12 months physiotherapy once a week
			3 years					3 year: normal cognitive development	
			6 years					6 year: normal cognitive development	
13	30	38	6 months	FOLFOX 4 cycles	Normal growth and development	No abnormalities	No neurological abnormalities	No details	No supportive care

*Below recommended fetal radiation exposure of 50 mGy.

OVERVIEW of examinations in INCIP follow-up study

Pediatric consultation: A general physical examination and neurological assessment performed by a pediatrician.

Cardiac assessment: 12-lead electrocardiograph (ECG) and a full echocardiographical assessment for structural and functional characteristics was collected by a cardiologist/experienced sonographer

Cognitive assessment: an age-adapted test battery for the assessment of intelligence, verbal and non-verbal memory, attention, working memory and executive functions by an experienced psychologist (Bayley Scales of Infant and Toddler Development, third edition (BSID-III), Child Behavior Checklist (CBCL), Behavior Rating Inventory of Executive Function – Preschool Version (BRIEF-P), Wechsler Preschool and Primary Scale of Intelligence, third edition (WPPSI-III), Subtask of Children's Memory Scale (CMS), Subtasks of Amsterdam Neuropsychological Tasks (ANT), Behavior Rating Inventory of Executive Function (BRIEF))

Table 3: Literature review: Case reports on chemotherapy for gastric cancer during pregnancy

Ref.	Number of cases	Patient age (years), AGP, gestational age at diagnosis (weeks)	Histology	Stage at diagnosis	Symptoms at diagnosis	Treatment	Period of treatment (gestational weeks)	Complications during pregnancy, Obstetrical outcome, Gestational age at delivery (weeks)	Weight at birth (grams), neonatal outcome	Maternal outcome (months after delivery)
Cift et al., 2011	Case 1	26, A0G2P1, 24	Poorly differentiated adenocarcinoma with signet-ring cell morphology	Stage Iv (bilateral adnexal masses)	Abdominal pain, nausea and vomiting	4 days of 5-FU (425 mg/m2 and 10 mg/m2 calcium folinat	29-29$^{4/7}$	Preterm contractions, spontaneous vaginal delivery, 29$^{4/7}$	930g, healthy	DOD (2 days)
Pacheco et al. 2016	Case 1	27, A0G3P2 12	Poorly differentiated adenocarcinoma with signet ring cell	cT3N3M1 (stage IV) (peritoneal metastasis)	Epigastric pain, weight loss	Palliative chemotherapy (5-FU (1000/m2) and cisplatin (75mg/m2) day 1,2,3,4 every 28 days, 4 cycles during pregnancy)	12-24	Preterm contractions, spontaneous vaginal delivery, 26	850g, Deceased (0.5m) due to respiratory failure	DOD (7m)
	Case 2	33, A0G2P1 15	Poorly differentiated adenocarcinoma with signet-ring cell morphology	cT3N0M0 (stage IIA) pT4aN3M0 (stage pIIIC)	Epigastric pain, weight loss	FOLFOX(oxaliplatin 85mg/m2, leucovor200mg/ m2, 5-FU (400mg/ m2 day1, 600mg/m2 day 1 and 2) every 14 days), 4 cycles during pregnancy, total radical gastrectomy after delivery, adjuvant chemoradiation	18-26	Preterm contractions, spontaneous vaginal delivery, 36	3150g, healthy	Deceased (41m)

Table 3: Literature review: Case reports on chemotherapy for gastric cancer during pregnancy (continued)

Ref.	Number of cases	Patient age (years), AGP, gestational age at diagnosis (weeks)	Histology	Stage at diagnosis	Symptoms at diagnosis	Treatment	Period of treatment (gestational weeks)	Complications during pregnancy, Obstetrical outcome, Gestational age at delivery (weeks)	Weight at birth (grams), neonatal outcome	Maternal outcome (months after delivery)
Kim et al. 2016	Case 1	36, AxGxPx, 18	unknown	Locally advanced stage	unknown	Totally laparoscopic distal gastrectomy followed by FOLFOX, 4 cycles during pregnancy	28-33	No complications, elective delivery 36	healthy	NED (12m)
Nishie et al. 2015	Case 1	>30y, AxGxPx, 23	Poorly differentiated adenocarcinoma, no HER2 overexpression	Stage IV (bilateral adnexal masses, cervical lymph node	Epigastralgia, left cervical lymph node swelling	2 cycles of Paclitaxel (50 mg/m2) on day 1 and 8 and S1* daily (100mg/body), Continued Cisplatin and S1 after pregnancy	24-33[4/7]	IUGR and peripheral neuropathy, elective cesarean section, 34 weeks	1442g, healthy	Progressive disease with meningitis carcinomatosis, DOD (6.3m)

S1*: tegafur (=prodrug of active substance 5-FU), gimeracil, oteracil

APG: Abortion(miscarriage)/Gravidity/Parityase

DOD: Dead of dise

NED: no evidence of disease

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.[3] 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.[8,9]

In the literature we identified five patients receiving a 5-FU-based regimen for advanced gastric cancer during pregnancy, with re-assuring fetal outcomes.[11-13] Details are summarized in Table 3. 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.[14] 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).[14]

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.[3,8,9]

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).[15] Young patients are reported to have lower overall survival compared to patients > 40 years of age if curative resection is not achieved.[15] 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. [16] 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.[5] 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.[17]

Estrogen receptors (ER) are found in about 20-30% of human gastric cancers, mainly in the poorly differentiated type.[8] 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.[18] 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.[7,19] 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 4.[19-29] 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.

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 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.[30] 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.[7] 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).

Table 4: 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)	Reference	Clinical data	Reference
5-FU (Fluorouracil)	MW*: 130 g/mol Negligible PB (8-12%)	28% *(rat model)*	Boike et al [20]	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. [19] Cardonick et al. [25]
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. [25]
Platinum-derivates					
Oxaliplatin	MW*: 397 g/mol High PB (>90%)	No data	Al-Saleh et al [21] Van Calsteren et al. [22]	Few case reports on oxaliplatin (one case of neonatal hypothyroidism in 8 patients treated with FOLFOX for colorectal cancer) Reports of hearing loss when cisplatin used during pregnancy. Carboplatin appears to be a safer alternative.	Pellino et al. [26] Amant et al. [19]
Cisplatin	MW*: 298 g/mol, High PB (>90%)	2-24% *(ex vivo placental perfusion model)*			
Carboplatin	MW*: 371 g/mol Limited PB (25-40%)	up to 57% *(baboon model)*			
Epirubicin	MW*: 543 g/mol Moderate PB (~77%)	Less than 10% *(baboon model)*	Van Calsteren et al. [23]	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. [19] Cardonick et al. [25]

Table 4: Pre-clinical and clinical data on placental transfer for most common cytotoxic drugs used for gastric cancer (continued)

Drug	Drug characteristics[Δ]	Pre-clinical data (placental transfer)	Reference	Clinical data	Reference
Taxanes					
Paclitaxel Docetaxel	MW*: 854 g/mol High PB (89-98%) MW*: 808 g/mol High PB (94-97%) *Drug efflux by placental p-glycoprotein transporter*	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. [22] Berveiller et al. [24]	Favorable toxicity profile in small case series when administered during second or third trimester of pregnancy (12-25 patients)	Cardonick et al [27]
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. [22]	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. [28]

[Δ]Reference for drug characteristics: Drugbank 5.0 [29]

*Agents with low molecular weight (<500 g/mol) and low protein binding will easily cross 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

Current recommendations for the management of pregnant patients with a diagnosis of gastric cancer is based on available case series.[3,5,8] 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 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.[11-14,26] 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.[19] 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.

Supporting information (Table S1) related with this article can be found in the online version at doi: 10.1111/aogs.13731

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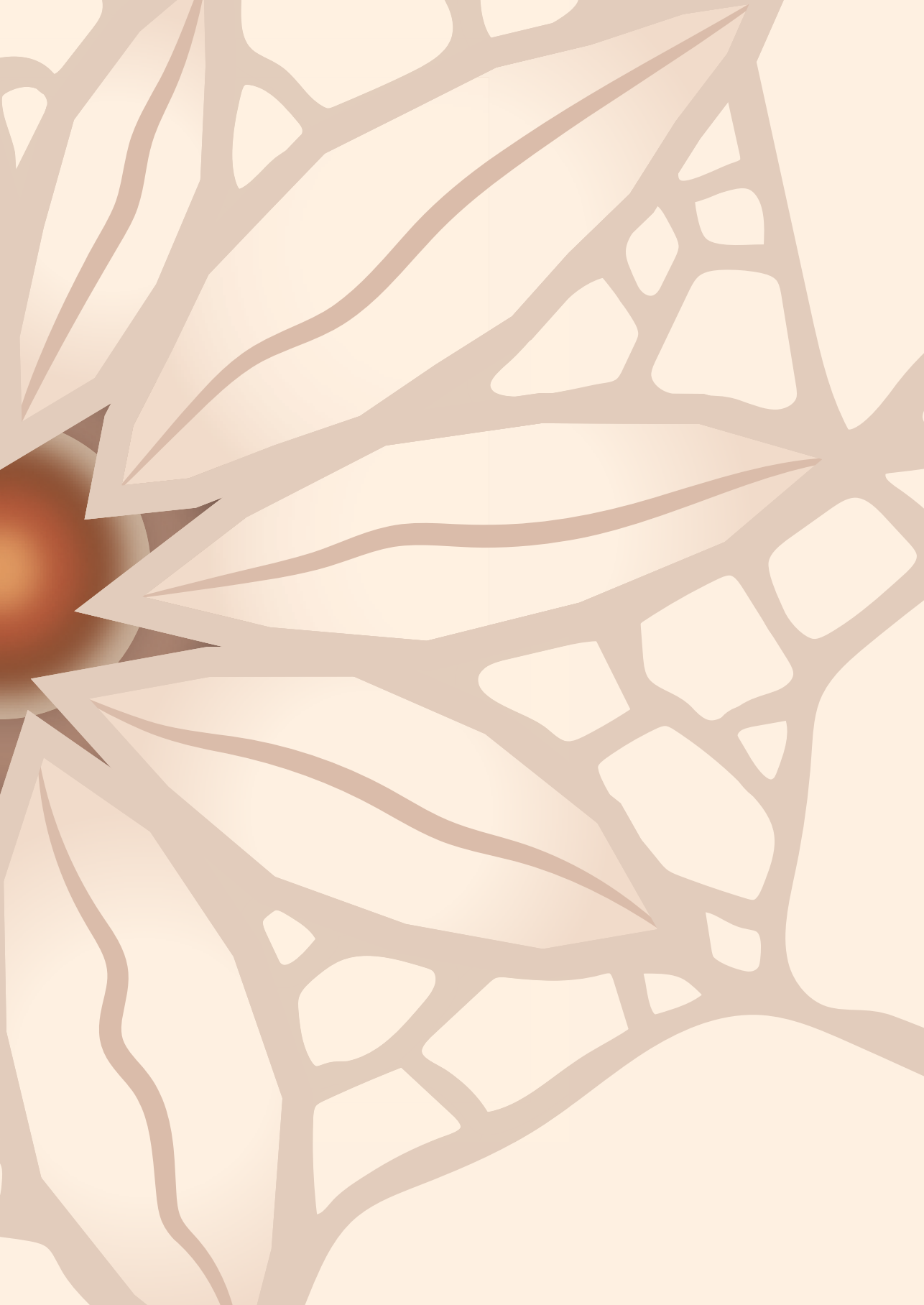

Chapter 7.

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 live births (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).[1,2] Breast cancer, melanoma, hematological, and cervical cancer are the most common types of cancer diagnosed during pregnancy.[1,3] With the increasing awareness of the feasibility of antenatal cancer treatment, fewer pregnancies are terminated and more pregnant women receive chemotherapy.[4] 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.[5] 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.[6,7] In oncological care, it is used to treat or prevent prolonged grade 3 (absolute neutrophil count (ANC) < 1.0×10^9 /L) and 4 (ANC < 0.5×10^9/L) neutropenia or febrile neutropenia (grade 3–4 neutropenia with fever) in patients receiving chemotherapy.[8,9] In patients with high risk breast cancer, dose dense chemotherapy regimens with G-CSF support, are considered standard of care.[5,10]

As available data are still limited to case reports and small case series, use of antenatal G-CSF is still debated.[11,12] 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 preven-

tion 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).[8] Neutropenia was divided in grade 1–2 (mild) (absolute neutrophil count (ANC) 1.5 × 10^9/L—lower limit of normal (LLN) or ANC 1.0–1.5 × 10^9/L, respectively) and grade 3–4 neutropenia (ANC of 1.0–0.5 × 10^9/L or below 0.5 × 10^9/L, respectively). Febrile neutropenia was defined as an ANC below 1.0 × 10^9/L and fever (=>38°C). Grade 3–4 leukopenia was defined as a white blood cell count (WBC) below 1.0 × 10^9/L), thrombocytopenia was divided in grade 1–2 (mild) [platelets count (PC) < 150 × 10^9/L) and grade 3–4 (severe) (PC < 50 × 10^9/L).[8] 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 h after delivery. Neonatal neutropenia was defined as absolute neutrophil count (ANC) < 1.0 × 10^9/L, leukopenia as white blood cell count (WBC) < 5.0 × 10^9/L, thrombocytopenia as PC < 15 × 10^9/L, and anemia as Hb less than 14 g/dL.[8,13-17] Customized percentiles for birth weight (p) were calculated, adjusted for GA at delivery, parity, ethnicity, body mass index (BMI), and sex of the infant.[18] Neonates were small for gestational age (SGA) if the birth weight was below the 10^{th} 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 Supplementary Table S1 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).

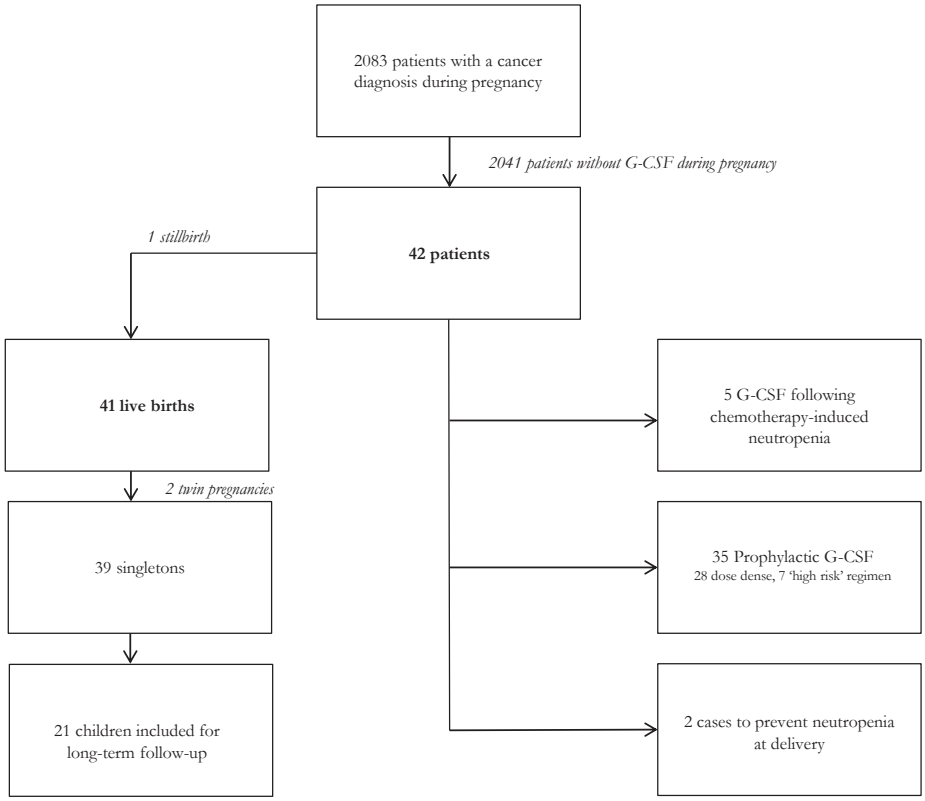

Figure 1. Study flow chart

Table 1: Maternal characteristics (n=42)

Maternal characteristics	**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

Table 1: Maternal characteristics (n=42) (continued)

	Number	**%**
Chemotherapy		
Anthracycline-based	18	42.9
Anthracycline-based with taxanes	15	35.7
Other**	9	21.4
	Median	**Range**
Gestational age at first 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

*for 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)

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%).

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.

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

Maternal blood results	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
Anaemia	16	67	14	58	2	8

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

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 < 0.1×10^9/L) following vincristine, ifosfamide, doxorubicin, etoposide (VIDE) chemotherapy. Two patients received rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone (R-CHOP) with pegfilgastrim and did not develop hematological toxicities, except for mild anemia in one patient.

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 5-fluorouracil, epirubicin, cyclophosphamide (FEC) 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)

Obstetric outcomes	**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 hemorraghe	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 live births 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).

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

Neonatal outcomes	**Median**	**Range**
Birth weight (grams)	2855	850-3780
	n	**%**
Customized birth weight 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
Anaemia****	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.

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 5-FU, epirubicin, cyclophosphamide (FEC) (+ pegfilgastrim) and docetaxel from 20 weeks of pregnancy onwards, was born with an absent uvula. The other neonate, prenatally exposed to dose dense doxorubicin, cyclophosphamide (AC) 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.

One women delivered of healthy twins following induced labor at 37 weeks after dose dense epirubicin, cyclophosphamide (EC) 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) (Supplementary Table S1). 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 birth weight of 2060 g (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 who 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.[19] 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.[20] 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.[21] 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.[19,22] Moreover, patients with severe congenital neutropenia treated with G-CSF, are at long-term risk to develop myelodysplastic syndrome and acute myeloid leukemia.[23] 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).[24,25]

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.[26] 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.[27] 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.[26,28-35] 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.[36,37] Furthermore, it is suggested that G-CSF can be administered in pregnancy or lactation in order to mobilize stem cells for stem cell transplantation.[38] 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 who received G-CSF just before delivery were shown to have increased neutrophil counts compared to a control group.[7] 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).[15] 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.[39]

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).[4] Major congenital malformations are estimated to occur in 255 out of 10,000 births (2.5%).[40] 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).[41] 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 according to EUROCAT).[4,42] In total, 22 (3.0%) major and 13 (1.8%) minor congenital malformations were seen in the offspring of 726 women treated with chemotherapy in the second and third trimester of pregnancy (*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%).[43] 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.[44] 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%).[43] 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.[45] 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.[46] 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.[12] 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.[47]

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.[11,12] 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.

CONCLUSIONS

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 safeguard cancer outcomes.

SUPPLEMENTARY APPENDIX

Supplementary Table 1: Pediatric follow-up of children prenatally exposed to G-CSF (n=21)

Case	GA at diagnosis (weeks + days)	GA at delivery (weeks + days)	GA at start treatment (weeks + days)	Chemotherapy during pregnancy (# of cycles)	G-CSF (administrations)	Diagnosis	Age at follow-up	General outcome	Cardiac outcome	Neurological outcome	Cognitive outcome
1	15+5	38+2	21+6	EC q3w *(4)* Paclitaxel q1w (7)	Peg (4)	Breast Cancer	18 months	Normal, delay in motor development	*	0	0
							3 years	0	0	0	0
2	30+3	37+1	33+4	EC q3w(1)	Peg (1)	Breast Cancer	18 months	*	*	*	Delay in cognitive development
							3 years	*	0	*	0
							6 years	0	0	0	0
3	21+4	37+3	21+5	RC q3w (6)	Peg (2)	Non hodgkin lymphoma	18 months	Normal, delay in motor development	*	0	0
							3 years	0	0	0	0
4	25+1	34+2	25+3	AC q3w (3)	Peg (?)	Breast Cancer	18 months	0	0	0	0
							6 years	0	0	0	0
							9 years	0	0	0	0
5	7+0	35+4	17+1	FAC q3w (6)	Peg (2)	Breast Cancer	18 months	*	0	*	0
							6 years	*	0	*	0
							9 years	0	*	0	0
6	7+5	35+4	16+1	EC q2w (4) Pac q1w (1) Doc q3w (3)	Peg (4)	Breast Cancer	18 months	0	*	0	0
							3 years	Overweight, normal development	0	0	Delay in cognitive and language development

Supplementary Table 1: Pediatric follow-up of children prenatally exposed to G-CSF (n=21) (continued)

Case	GA at diagnosis (weeks + days)	GA at delivery (weeks + days)	GA at start treatment (weeks + days)	Chemotherapy during pregnancy (# of cycles)	G-CSF (adminis-trations)	Diagnosis	Age at follow-up	General outcome	Cardiac outcome	Neurological outcome	Cognitive outcome
7	15+4	38+3	20+4	Doc q2w (3)	Peg (5)	Breast Cancer	18 months	0	*	*	Delay in cognitive development
							3 years	0	0	0	0
							6 years	0	0	0	0
8	18+0	36+1	18+5	R-ACVBP q3w (4) R-IE q3w (2)	Fil (?)	Non hodgkin lymphoma	18 months	0	*	0	0
9	6+2	36+6	12+6	AC q2w (4) Pac q1w (12)	Peg(4)	Breast Cancer	3 months	0	0	0	*
10	30+2	36+5	31+2	AC q2w (3)	Peg (3)	Breast Cancer	2 months	0	0	0	*
11	29+6	38+5	31+5	AC q2w (3)	Peg (3)	Breast Cancer	6 months	0	0	0	*
							14 months	0	*	0	0
12	28+1	36+0	*28+5*	AC q2w (3)	Peg (3)	Breast Cancer	18 months	0	0	0	Normal cognitive development for his premature age
13		38+2	35+0	AC q2w (2)	Lip (2)	Breast Cancer	3 years	0	0	0	0
14	22+3	37+2	39+6	AC q2w (4)	Peg (4)	Breast Cancer	3 years	0	0	0	0
15	17+6	37+4	22+1	AC q2w (4) Pac q1w (7)	Lip (4)	Breast Cancer	11 months	Normal, delay in motor development	0	0	*
							18 months	0	*	0	0

Supplementary Table 1: Pediatric follow-up of children prenatally exposed to G-CSF (n=21) (continued)

Case	GA at diagnosis (weeks + days)	GA at delivery (weeks + days)	GA at start treatment (weeks + days)	Chemotherapy during pregnancy (# of cycles)	G-CSF (administrations)	Diagnosis	Age at follow-up	General outcome	Cardiac outcome	Neurological outcome	Cognitive outcome
16	17+5	36+5	18+1	AC q2w (4) Pac (9)	Lip (4)	Breast Cancer	12 months	0	0	*	*
							18 months	0	*	0	*
17	16+6	37+0	22+1	AC q2w (4) Pac (6)	Lip (4)	Breast Cancer	18 months	0	0	0	0
18	16+1	37+1	18+3	AC q2w (4) Pac (9)	Lip (4)	Breast Cancer	18 months	0	*	0	0
19	16+5	38+3	18+1	R-CHOP q2w (6)	Peg (?)	Non hodgkin lymphoma	3 years	*	*	*	0
							6 years	0	0	0	0
20	15+2	29+2	16+0	R-CHOP q2w (6) VIM q1w (1)	Peg (?)	Non hodgkin lymphoma	18 months	0	0	0	Normal cognitive development, delay in language development
21	14+6	38+2	16+1	AC q2w (4) Pac q1w (8)	Lip (4)	Breast Cancer	18 months	Normal, delay in motor development	*	0	0
							3 years	0	0	0	0

Supplementary Table 1: Pediatric follow-up of children prenatally exposed to G-CSF (n=21) (continued)

Case	GA at diagnosis (weeks + days)	GA at delivery (weeks + days)	GA at start treatment (weeks + days)	Chemotherapy during pregnancy (# of cycles)	G-CSF (adminis-trations)	Diagnosis	Age at follow-up	General outcome	Cardiac outcome	Neurological outcome	Cognitive outcome

0: Normal development (in pediatric consultation), no abnormalities in cardiac outcome and neurological outcome, normal cognitive development

*: Data not available

All breast cancers are invasive ductal adenocarcinoma

Abbreviations chemotherapy: AC: doxorubicin-cyclophosphamide; doc: docetaxel; EC: epirubicin-cyclophosphamide; FAC: fluorouracil-doxorubicin-cyclophosphamide; pac: paclitaxel; R-CHOP: rituximab+cyclofosfamide+doxorubicine+vincristine + prednisone; R-ACVBP: rituximab, doxorubicin, cyclophosphamide, vindesine, bleomycin + prednisone; R-IE: Rituximab, Ifosfamide, Etoposide; VIM: ifosfamide, mitoxantrone;

General abbreviatons : GA: gestational age; q1w: every week; q2w: every 2 weeks; q3w: every 3 weeks; ?: unknown number of cycles/administrations; G-CSF: fil: filgrastim; lip: lipefilgrastim; peg: pegfilgrastim

OVERVIEW of examinations in INCIP follow-up study

Pediatric consultation: A general physical examination and neurological assessment performed by a pediatrician.

Cardiac assessment: 12-lead electrocardiograph (ECG) and a full echocardiographical assessment for structural and functional characteristics was collected by a cardiologist/experienced sonographer.

Cognitive assessment: an age-adapted test battery for the assessment of intelligence, verbal and non-verbal memory, attention, working memory and executive functions by an experienced psychologist (Bayley Scales of Infant and Toddler Development, third edition (BSID-III), Child Behavior Checklist (CBCL), Behavior Rating Inventory of Executive Function – Preschool Version (BRIEF-P), Wechsler Preschool and Primary Scale of Intelligence, third edition (WPPSI-III), Subtask of Children's Memory Scale (CMS), Subtasks of Amsterdam Neuropsychological Tasks (ANT), Behavior Rating Inventory of Executive Function (BRIEF))

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Chapter 8.

Gynecologic cancers in pregnancy: guidelines for pediatric care based on a third international consensus meeting

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NEONATAL AND PEDIATRIC CARE

The neonate needs to be examined thoroughly by a neonatologist or pediatrician. After exposure to chemotherapy, hematological parameters, liver and renal function should be checked. Preterm and small for gestational age (SGA) infants require specific neonatal follow up care. In case of cardiotoxic treatment (e.g. anthracyclines) administered during pregnancy, an echocardiogram in the first weeks is advisable. After platinum exposure, special attention for hearing function is needed throughout infancy.[1] It is anticipated, based on animal models as well as childhood cancer studies, that combining platinum exposure with aminoglycosides or furosemide is adding to the risk.[2,3]

Long-term toxicity data after chemotherapy exposure in young children with childhood cancer has shown cardiotoxicity, hearing loss, neurocognitive problems, endocrine impairment, secondary malignancy and general burden of disease.[4-7] In particular, anthracyclines are notorious for long-term cardiotoxicity in cancer survivors, and cisplatin for irreversible hearing loss.[6,7] Based on these findings surveillance guidelines have been developed for life-long follow up of young cancer survivors.[8]

Although it is still unclear whether the effects of *in utero* chemotherapeutic exposure are similar to the effects of exposure in young children with cancer, it is important to address the same short- and long-term toxic effects. Several important large-scale studies have addressed the outcome of children born to mothers diagnosed with cancer, but none have specifically investigated outcome in gynecological cancers. These studies have shown that middle- and long-term cognitive and physical outcomes of children prenatally exposed to chemotherapy appear reassuring till now.[9-15] Although neurocognitive problems and cardiotoxicity may become more apparent later in life. In addition, in prenatally platinum exposed children, irreversible hearing loss has been described.[1,16,17] Thus, we recommend a long-term follow up of children exposed antenatally to chemotherapy every three years, in case of cisplatin or anthracycline in utero exposure. Additionally, we recommend an auditory evaluation and echocardiographic follow up, respectively (Table 1).

Furthermore, a consultation shortly after birth as a standard of care, to (ideally) confirm that the newborn is healthy, to inform the families regarding follow-up, and to support them by giving information and access to specialized medical surveillance and psychosocial family care, is recommended. This is further underscored by the fact that, in the following years a probability exists that the child will lose the mother at an early age; hence the team can anticipate that psychosocial support may be offered, when desired.

Table 1: Follow-up of children born, after gynecological cancer in pregnancy

Cancer in pregnancy	**Screening of children with intra-uterine chemotherapy / radiotherapy during pregnancy because of maternal gynecological cancer (including cervix carcinoma, ovarian cancer and breast cancer)**													
Birth														
Examination of placenta	**X**													
Examination of neonate	**X**													
Registration of family (mother and child) (signed informed consent)	**X**													
Follow-up/Check-up (Care)		**X/X**[a]						**X**	**X**	**X**	**X**	**X**	**X**	**X**
Blood count (morphology, differentiation)[b]	**X**													
Evaluation of auditory function[c]		**X**								**X**				
ECG and echocardiogram[d]		**X**				**X**		**X**	**X**	**X**		**X**		**X**
Neurocognitive development (psychologist)		**X**						**X**	**X**	**X**	**X**	**X**	**X**	**X**
Neuromotor development (qualified physiotherapist/neurologist or pediatrician)		**X**						**X**	**X**	**X**	**X**	**X**	**X**	
Genetic consultation offered		**X**												
Time														
Months	**At birth**	**1-6**	**8**	**9**	**10**	**12**	**15**	**18**						
Years						**1**			**3**	**6**	**9**	**12**	**15**	**17**

The expert panel recommends the following roles for the multidisciplinary team involved in the follow-up: *Gynecologist*: Sends placenta for extensive pathological/histological examination (explicitly asks to examine for metastasis of maternal malignancy). Asks consultation of neonatologist. Consultation form: malignancy mother, moment of diagnosis, stage of the disease, metastasis, type, TCD and time of treatment. *Neonatologist*: Physical examination of the neonate, explanation of risk of metastasis and necessity to examine the placenta, reasons for follow-up. Monitor outcome of placental examination, contact parents with result, and perform additional diagnostic tests if indicated. Contact pediatrician experienced in chemo related toxicity, connected to INCIP. *Pediatrician* experienced in chemo related toxicity, connected to INCIP: further follow-up child. Perform surveillance including additional diagnostic.

[a]Intensive follow-up when indicated: placenta positive for micrometastasis or when neonatal abnormalities suspicious for metastasis are identified at birth. [b]Diagnostic tests: i) laboratory tests will include complete blood count when chemotherapy was administered <4 weeks prior to the birth (risk of bone marrow depression) or complete blood count plus

analyses of transaminases and Lactic Acid Dehydrogenase (LDH) (when the placenta contains metastasis or when neonatal abnormalities suspicious for metastasis are found); ii) abdominal ultrasound when the placenta contains metastasis (in the first week of life), or when neonatal abnormalities suspicious for metastasis are identified (urgently in the first days postpartum).

[c]After intra-uterine exposure to platinum-based treatment: Evaluation of auditory function by ALGO/OAE: until 6 years. Beyond the age of 6 years a tone audiogram is advised.

[d]Echocardiogram and Electrocardiogram: after intra-uterine anthracycline exposure.

TCD, total cumulative dose; OAE, oto-acoustic emissions; ALGO, auditory brainstem response assessment

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Chapter 9.

Discussion, perspectives and future challenges

…. While the mother received chemotherapy; the baby was doing well and growing. Labor was induced at 39 weeks and 1 day of pregnancy. This was two and a half weeks after the last administration of the fifth cycle of R-CHOP. A baby boy was born with a birth weight of 3360 grams (50th percentile) and an APGAR of 10 at 1 and 5 minutes. The neonatal physical examination was normal. Histology of the placenta showed a normal placenta and no metastasis of the maternal cancer were found. The baby went home in good condition. After the last cycle of R-CHOP postpartum, the mother showed a clinical complete response. When the child reached the age of 7 months, the parents had their first follow up visit at the Cancer In Pregnancy Outpatient Clinic of the Princess Maxima Center in Utrecht. The physical examination of the baby was normal and biometric data showed that his growth was within the normal curve. A cardiac evaluation with electrocardiogram (ECG) and echocardiographic examination was performed, and motor development was evaluated by a physiotherapist. No structural cardiac defects were identified. He had an appropriate motor development. At 18 months and 36 months of follow-up, he again showed an appropriate cognitive, motor and behavioral development for his age. At 36 months of follow-up, a cardiac evaluation with ECG and echocardiographic examination was again performed. No structural cardiac defects were identified. The family look back to the darker moments of the diagnosis and the start of the treatment almost four years ago. They could hardly have dared dream of this outcome: a healthy mother and son. It reminds them of how incredibly special their boy is.

NEONATAL OUTCOME

In this thesis, an analysis on congenital malformation occurrence according to gestational age at chemotherapy exposure in 755 pregnant patients is presented. This series indicates that chemotherapy prior to 12 weeks of gestation is associated with an increased risk of congenital malformations, with the highest risk when the first exposure occurred around the time of conception and continued during the first 12 weeks of gestation. In case of exposure after 12 weeks of gestation, the congenital malformation rate was 4.8% overall, which is comparable to the expected rates in the general population (between 2.5 to 6.9% for major malformations and 6.5 to 35.8% for minor abnormalities).[1-3]

These observational data suggest that chemotherapy can be initiated from 12 weeks of gestation onwards. However, the implementation of our findings in clinical practice will require some careful considerations. Firstly, accurate timing of conception and dating by ultrasound is crucial for appropriate management. The timing of conception may be uncertain because of irregular menstrual cycles and the inter-individual differences surrounding the developmental steps in embryogenesis.[4] Therefore, in early pregnancy the introduction of a safety period of 1 week can be considered to further minimize the risk of chemotherapy-induced congenital malformations. Our results suggest a high cytotoxic-related risk of structural congenital malformations after chemotherapy exposure prior to 12 weeks of gestation; there is hence no evidence to suggest a negative impact of delaying the start of chemotherapy to after 14 weeks of gestational age, as recommended previously.[5] Nevertheless, as documented in this series, a normal neonatal outcome without short-term birth defects is possible after exposure to chemotherapy before 12 weeks of gestation. Furthermore, parents may opt to preserve the pregnancy and prenatally screen for fetal malformations. Non-invasive prenatal testing (NIPT) is not conclusive in cancer patients as tumor cell-free DNA will interfere with the results.[6] If certainty on chromosomal abnormalities is desired, an amniocentesis for karyotyping can be offered, before the initiation of cancer treatment.[7]

In the 6-year-old cohort, 18 children (14.9%) were born small for gestational age (SGA) versus 7 children (5.9%) in the control group. Children exposed to chemotherapy were at a higher risk for SGA than non-exposed children or children exposed to surgery or radiotherapy. In the case series of 39 children prenatally exposed to chemotherapy and Granulocyte colony-stimulating factor, 11 children (28%) were SGA. In the case series of 10 children prenatally exposed to gastric cancer during pregnancy, four children (two exposed to chemotherapy and two non-exposed) were SGA. SGA in the gastric cancer exposed children might be explained by the poor maternal general nutritional status inherent to gastric cancer. However, the exact etiology of developing SGA in pregnancies complicated with a cancer diagnosis needs further research.

The incidence of neonatal intensive care unit (NICU) admission is also common in pregnancies complicated with cancer. In the case series of 10 children prenatally exposed to gastric cancer during pregnancy, nine children were admitted to the NICU. In the G-CSF series, 16 neonates (41%) were admitted to the NICU. In both series, most neonates were admitted to NICU because of prematurity.

COGNITIVE OUTCOMES

Ongoing inclusion of the cohort allowed us to perform a detailed analysis on our 6-year-old study cohort. In total, 132 study children and 132 matched controls were included. Although no significant differences were identified in most cognitive functions, children from the cancer in pregnancy group and a subgroup of chemotherapy-exposed children scored on average 6 points lower on Verbal IQ than their matched controls. A study on preterm infants showed that increased amount of being spoken to by their parents during their stay at the neonatal intensive care unit may contribute to higher cognitive and language outcomes at 7 and 18 months corrected age.[8] In the case of cancer during pregnancy, mother-child interactions in the neonatal period and early years of life may be more restricted due to impact of the maternal disease and treatment or even absent in the case of maternal death. This could have an effect on general cognitive development and, more specifically, on language development. Our data support this hypothesis, as Verbal IQ was more affected in children whose mothers died than in children with surviving mothers. Furthermore, the visuospatial long-term memory score was significantly lower in the study group and in the chemotherapy-exposed subgroup compared to their matched controls, although attention, memory span and short-term memory were not affected. This is in contrast with studies on childhood cancer survivors mostly reporting working memory and attention deficits and slower information processing speed.[9]

Heterogeneity of the study group may mask significant differences in smaller subgroups and underscores the need for further research to identify whether specific subgroups of children born to women with a cancer diagnosis during pregnancy are at higher risk of developmental problems. It is possible that these effects are only seen in a small subgroup of these children or at specific ages, or following specific family, or motherhood conditions. Investigating the impact of motherhood conditions, an analysis of 57 children exposed to hematological maternal cancer with or without treatment was performed. Neurodevelopment outcomes at a median age of 6.1 years were normal and reassuring in both the group with and without treatment. These reassuring data support the current policy to treat hematological cancer during pregnancy, instead of delaying until after delivery. The median follow-up period of children prenatally exposed to hematological cancers was 6.1 years and may have been too short to identify neurocognitive problems that become more

apparent at later school-ages. In addition, in a multimodal MRI study, prenatal exposure to maternal cancer and its treatment was associated with changes in local grey and white matter structure, but not functional connectivity or global organization.[10] Moreover, the study group was small and postnatal environmental factors challenge the research on the long-term neurodevelopmental outcome of prenatal exposure to hematological cancers during pregnancy. Hence, longitudinal accrual of our children at all ages and subgroup analyses are needed for a better understanding of the possible long-term cognitive consequences.

EMOTIONAL PROBLEMS

Parents of children prenatally exposed to chemotherapy reported more difficulties related to emotional control of their children than parents of children in the control group. Cancer during pregnancy is a challenging life event that may cause prenatal maternal stress. Children exposed to antenatal maternal anxiety reported more overall problems in behavior, emotional symptoms, peer relationship problems, conduct problems and less prosocial behavior at age five.[11] Another contributing factor might be prenatal and postnatal bonding, which might be at risk in case of cancer during pregnancy. Parents have to deal with uncertainty, feelings of guilt, questions and anxieties, which could lead to emotional difficulties in the mother-child relationship.[12] Earlier studies have highlighted the importance of the early mother-child relationships for the child's cognitive and emotional development. [13] In addition, in subgroup analyses of children prenatally exposed to hematological malignancies, the needs of supportive care in the child was associated with the loss of the mother. These results suggest that during follow-up for these children, surveillance of emotional development is important. Early screening of emotional development may prevent difficulties in emotion regulation.

CARDIAC OUTCOMES

In 2019, we compared the values of ECG and echocardiographic assessments between our study cohort of 6-year-old children and the control cohort. We found higher diastolic blood pressure in 78 chemotherapy-exposed children versus control children and in a subgroup of 59 anthracycline-exposed versus control children. Previous analysis in our cohort in 2012 and 2015 also revealed small but significant differences in diastolic variables and echocardiographic measurements.[14] Collectively, these data may suggest the presence of differences in cardiac measurements in children exposed in utero to chemotherapy in comparison to those unexposed. The cardiotoxic effect of anthracyclines is well known and

maternal conditions such as poor maternal nutrition may also lead to cardiac disorders in the offspring later in life.[15,16] Although the higher diastolic blood pressures in the study group were all within normal range and no patients had abnormal values, it is too early to consider this as reassuring, especially since children with cancer exposed to anthracyclines can develop subclinical and clinical cardiomyopathy, even decades after their cancer treatment.[17] This highlights the need for an increase of the cohort and longer follow-up.

OTOTOXICITY

Platinum-based chemotherapy is commonly used in the treatment of cervical cancer, the third most common cancer type during pregnancy. As platinum-based chemotherapy can lead to ototoxicity in cancer survivors, we performed audiograms on 8/14 children prenatally exposed to cisplatin.[18] We found that 3/8 children revealed bilateral hearing loss; one child had bilateral hearing loss diagnosed at birth (at 6 months up to 50 dB at 3000Hz), one child had bilateral hearing loss in low and high regions (up to 50db) diagnosed at the age of 6 years and one child had hearing loss in the high regions (up to 100 dB at 8000Hz) diagnosed at the age of 6 years.[19] This suggests that ototoxicity in the children exposed to antenatal platinum-based chemotherapy may be as relevant as in childhood cancer patients, where around 50% of the cisplatin-treated cases suffer from serious irreversible hearing loss, with its associated consequences for speech-, cognitive and social development.[20] In children with cancer, risk factors for hearing loss are younger age and genetic susceptibility, as well as the use of co-medication.[21] Thus, prospective standard surveillance of auditory function of children prenatally exposed to platinum-based treatment is advised, similar to the advice in childhood cancer survivors.[22]

UPCOMING PERSPECTIVES AND FUTURE CHALLENGES

The results of the follow-up studies are currently reassuring for the development of the children prenatally exposed to maternal cancer, the associated stress, diagnostic imaging and treatments. The studies presented showed that antenatal chemotherapy is possible and safe after the first trimester. However, subtle differences in the development of children emphasize the need for long-term follow-up. We hypothesize that subgroups within the cohort of children prenatally exposed to maternal cancer and or its treatment might be more at risk for problems than others.

One possibility is that the type of chemotherapy might influence whether children are at risk of specific developmental problems. Chemotherapy exposure in childhood can-

cer patients can lead to cardiotoxicity and neurocognitive problems later in life.[16,23] In particular, anthracyclines are notorious for long-term cardiotoxicity in cancer survivors, whereas cisplatinum chemotherapy is related to ototoxicity in adults and children with cancer.[21,24] So, it might be conceivable that antenatal exposure to specific chemotherapies have substantial neuropsychological, cardiac or auditory effects.

Another possibility is that the development of these children is affected by specific maternal conditions during pregnancy or postpartum that are the result of the cancer diagnosis and treatment. Roseboom et al. demonstrated the fundamental importance of a good start during the first 1000 days after conception.[25] Cancer or cancer treatment represents a physical and psychological burden for pregnant women; this can lead to stress, anemia, malnutrition and lack of parental attachment during pregnancy and postpartum.[26] For instance, the conflicting emotions experienced by pregnant cancer patients as well as maternal depressive symptoms can have a negative impact on both prenatal attachment and the mother-child relationship during the post-partum period. Monitoring of the parental and infant psychological and emotional well-being may be helpful. In addition, in utero exposure to poor maternal nutrition can lead to cardiovascular and metabolic diseases in the offspring.[27] A subset of children exposed to cancer in pregnancy and treatment-related maternal conditions may thus be more at risk of presenting detrimental health effects in later life.

Further research is needed to investigate how long-term health effects in children born from women with a diagnosis of cancer during pregnancy could be attributable to exposure to specific chemotherapies and to maternal conditions associated with the cancer diagnosis and treatment. Follow-up until adulthood is recommended as the impact of cancer treatment during pregnancy on fertility and cancer development in the children is still unknown. To identify children at risk, large-cohort, longitudinal studies with an agreed core outcome set as well as clinical guidelines are of utmost importance.

Data on the long-term risks and safety of children prenatally exposed to maternal cancer and treatment are indispensable for patients and clinicians when considering cancer treatment during pregnancy. The data may help clinicians, patients and their families to make an informed decision about the start of cancer treatment during pregnancy. The outcomes of the children were generally reassuring, as the current thesis shows normal child development after maternal cancer diagnosis and treatment. In clinical practice, psychosocial support may be helpful for these children and follow-up until adulthood is advised.

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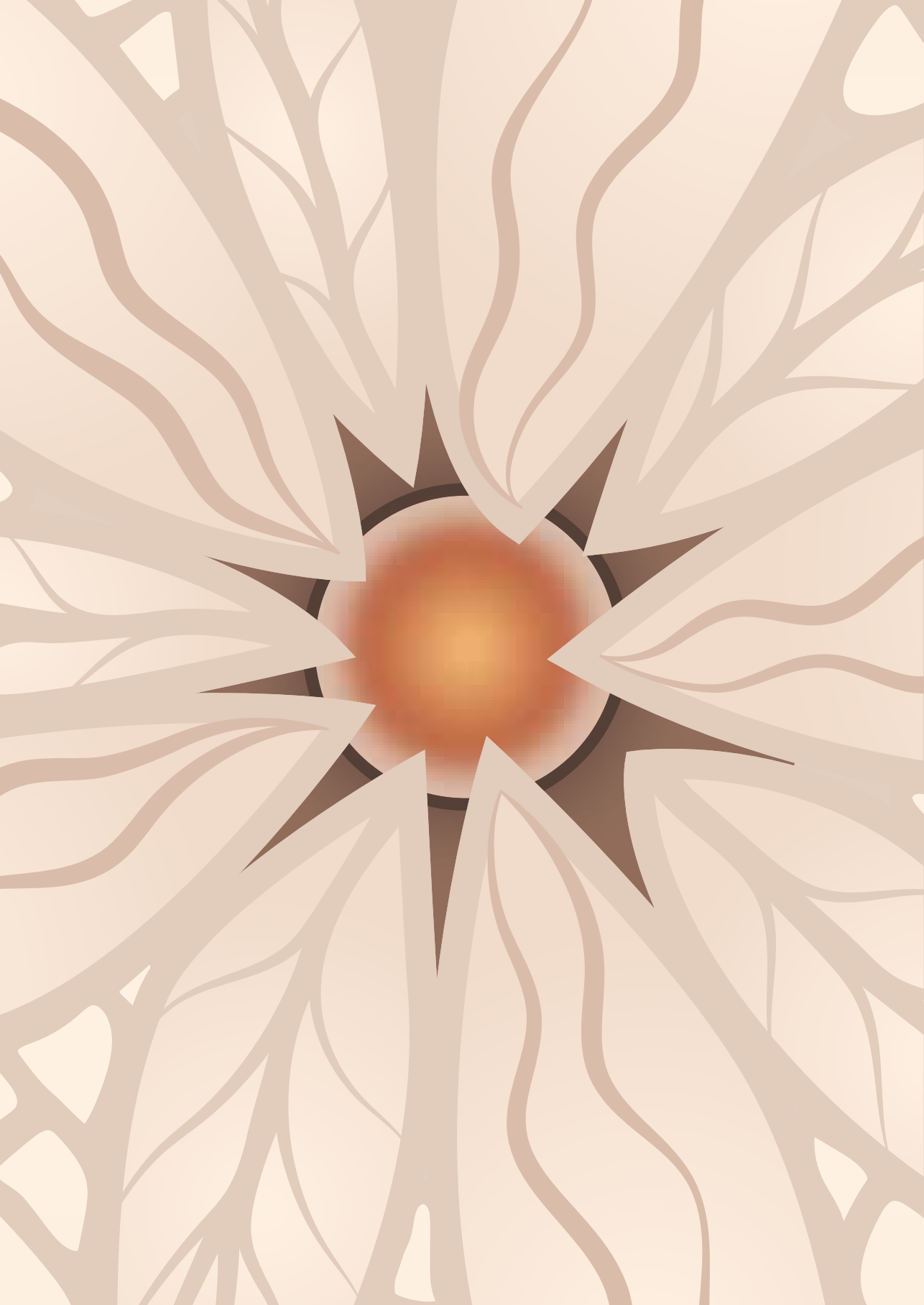

Chapter 10.

Summary & Samenvatting

CHILD DEVELOPMENT AFTER MATERNAL CANCER DIAGNOSIS AND TREATMENT DURING PREGNANCY

Data on the long-term impact of prenatal exposure to maternal malignancy and its treatment on the child's general health, cognitive, cardiac, behavioral and neurological development are scarce. To address the short and long term effects, children exposed to antenatal cancer and cancer treatment are followed in an international, multicenter, longitudinal study by the International Network on Cancer, Infertility and Pregnancy (INCIP). Starting in March 2005 at University Hospitals Leuven, Belgium, currently six European centers and one center in the USA participate collectively in this study using a harmonized follow-up protocol. In June 2018 the follow-up for Dutch children was nationally centralized in the Princess Máxima Center for pediatric oncology by establishing the outpatient expertise center for children born from pregnant woman with cancer, named the 'Cancer In Pregnancy outpatient clinic'. The focus of the research presented is to address the effects of prenatal exposure to maternal malignancy and its treatment, with a major focus on the neurocognitive development.

Chapter 2 describes the reported evidence regarding the management and the obstetric, neonatal and pediatric risks of cancer treatment during pregnancy. As a cancer diagnosis during pregnancy imposes a medical-ethical dilemma, the review describes the feasibility and safety of oncological treatment during pregnancy, in order to inform the patients about the possible risks for mother and child. Preterm delivery was common in pregnancies complicated by cancer and cancer treatment during pregnancy seems to be associated with low birth weight. Although short term follow-up of children prenatally exposed to cancer treatment was reassuring, long-term follow-up and prospective standard surveillance of children prenatally exposed to cancer treatment were recommended.

In **Chapter 3**, we aimed to investigate the gestational age at which chemotherapy can be safely considered during pregnancy, avoiding congenital anomalies. We observed that the occurrence of congenital malformations was the highest if first chemotherapy exposure was prior to 12 weeks of gestation, with the greatest risk if the exposure started around the time of conception. This led to the advice that chemotherapy, when necessary, can be initiated from 12 weeks of gestation onwards. If exact pregnancy dating is in doubt, a 1-week safety period should be added to dating based on ultrasound when making decisions on oncological management. We also observed that a considerable number of patients became incidentally pregnant while receiving chemotherapy. This underscores the importance of contraceptive advice and pregnancy testing in young women starting chemotherapeutic treatment.

Chapter 4 evaluated the largest cohort of children aged six prenatally exposed to maternal cancer, the associated stress, diagnostic imaging and treatments (including surgery, chemotherapy and radiotherapy). The health status, cognitive development and cardiac

structure and function of these children were assessed. In comparison to matched controls, no significant differences were found in Full Scale IQ, Performance IQ, Processing Speed, memory span, short-term memory, attention, behavior and cardiac structure and function. However, children from the cancer in pregnancy group and a subgroup of chemotherapy-exposed children showed lower Verbal IQ and visuospatial long-term memory outcomes as well as a higher, though not clinically relevant, diastolic blood pressure. We also documented ototoxicity in three children exposed to cisplatin and a higher risk for need for glasses. Furthermore, we were interested in the emotional regulation of 37 children prenatally exposed to chemotherapy. As reported by parents these children had more difficulties with effectively managing and responding to an emotional experience. Together, these studies found lower Verbal IQ and weaker emotional regulation skills in children prenatally exposed to chemotherapy compared to matched controls. Special attention to the cognitive and emotional development was advised. Moreover, long-term follow-up of the auditory function of children prenatally exposed to cisplatin is recommended. In both analyses the study group was heterogeneous as all types of maternal malignancies were included. Therefore, **Chapter 5** described the specific impact of maternal hematological malignancy and its treatment during pregnancy on the perinatal outcome, health status and neurocognitive development of the offspring. Prenatal exposure to hematological maternal malignancies with or without treatment did not affect the neurodevelopment of the child in the long-term. However, the need for supportive care in the child was associated with the loss of the mother. Therefore, surveillance of the emotional development of the child was advised, especially when the mother had died of cancer.

Chapter 6 elucidates the impact of the extremely rare condition of gastric cancer during pregnancy. In total, 8 out of 10 children were born preterm because of pre-eclampsia, maternal deterioration or therapy planning. All but one of the mothers deceased within two years after delivery. Data of the clinical follow-up of four children were available and, in the two cases for which a cardiac evaluation was performed, no abnormalities were observed. One child with neonatal complications developed residual cerebral palsy, epilepsy and hemianopia. Despite these symptoms requiring intensive physiotherapy, the child showed a good cognitive development at 15 months, 3 years and 6 years of follow-up. One child born at 34 weeks and 3 days of gestational age was cognitively assessed at 18 months of age and showed an adequate cognitive development when correcting for his prematurity at birth.

In **Chapter 7** the impact of Granulocyte colony-stimulating factor (G-CSF) for dose dense chemotherapy during pregnancy was evaluated. In total, 21 children with a median follow-up of 18 months were included in clinical follow-up and no neurological of functional cardiac abnormalities were reported. In four children, motor development was delayed, which required physiotherapy. In two premature children, a delayed cognitive development was identified.

Guidelines for neonatal and pediatric care for children exposed to gynecologic cancers are described in **Chapter 8.** We recommend a long-term follow-up of children prenatally exposed to chemotherapy and the need for a multidisciplinary approach in an experienced center where gynecologists, oncologists, neonatologists and pediatricians can easily be cooperatively involved in the management.

ONTWIKKELING VAN HET KIND NA MATERNALE KANKER EN KANKERBEHANDELING TIJDENS DE ZWANGERSCHAP

Er is nog weinig bekend over de lange termijn gevolgen van prenatale blootstelling aan maternale maligniteit en kankerbehandeling op de algehele gezondheid, cognitieve, cardiale, gedragsmatige en neurologische ontwikkeling van het kind. Om de korte en lange termijn effecten te onderzoeken, worden kinderen die zijn blootgesteld aan prenatale kanker en kankerbehandeling gevolgd in een internationale, multicenter en longitudinale studie van het International Network on Cancer, Infertility and Pregnancy (INCIP). Deze studie is in maart 2015 gestart in het Universitair Ziekenhuis Leuven te België en, wordt momenteel uitgevoerd in zes Europese centra en één centrum in Amerika, middels een geharmoniseerd follow-up protocol. In juni 2018 is de opvolging van de Nederlandse kinderen gecentraliseerd in het Prinses Máxima Centrum voor kinderoncologie. Er is een expertise spreekuur ingericht genaamd 'Cancer In Pregnancy', speciaal voor opvolging van de kinderen geboren uit deze zwangerschappen. In dit proefschrift worden de effecten van prenatale blootstelling aan maternale maligniteit en kankerbehandeling beschreven, met een primaire focus op de neurocognitieve ontwikkeling.

Hoofdstuk 2 geeft een overzicht van de huidige kennis van kanker en zwangerschap met aandacht voor de verschillende soorten behandelingen en de obstetrische, neonatale en pediatrische risico's van kankerbehandeling tijdens de zwangerschap. Kanker tijdens de zwangerschap vormt een medisch-ethisch dilemma. Om de patiënten zo goed mogelijk te kunnen informeren over de risico's voor moeder en kind worden in dit hoofdstuk de mogelijkheden en veiligheid tot oncologische behandeling tijdens de zwangerschap beschreven. Prematuriteit kwam vaak voor bij een zwangerschap die gecompliceerd werd met kanker en een oncologische behandeling tijdens de zwangerschap was geassocieerd met een lager geboortegewicht. De korte termijn gevolgen bij deze kinderen waren geruststellend maar lange termijn opvolging en standaard nazorg worden geadviseerd.

In **Hoofdstuk 3** onderzoeken we vanaf welke zwangerschapsduur chemotherapie veilig gegeven kan worden tijdens de zwangerschap zonder dat daarbij het risico op aangeboren afwijkingen toeneemt. Het risico op aangeboren afwijkingen was het hoogst als de eerste kuur chemotherapie vóór 12 weken zwangerschap werd gegeven, met het grootste risico wanneer de chemotherapie rondom de conceptie werd gegeven. Het advies is dan ook om wanneer chemotherapie nodig is, vanaf 12 weken zwangerschap te starten. Wanneer twijfel bestaat over de exacte zwangerschapsduur moet bij de beslissing over de start van chemotherapie, een marge van een week worden toegevoegd aan de zwangerschapsduur, waarbij de echo's moeten worden meegenomen in de besluitvorming voor de oncologische behandeling. Daarnaast werd een behoorlijk aantal patiënten ongemerkt zwanger

tijdens een behandeling met chemotherapie. Dit benadrukt het belang van advies over anticonceptie en routinematige zwangerschapstesten bij jonge vrouwen die starten met chemotherapie.

Hoofdstuk 4 beschrijft het grootste cohort van kinderen van zes jaar oud die prenataal werden blootgesteld aan maternale kanker, de bijbehorende stress, diagnostische beeldvorming en behandelingen (inclusief chirurgie, chemotherapie en radiotherapie). De algehele gezondheid, cognitieve ontwikkeling en structuur en functie van het hart werden beoordeeld. In vergelijking met de gematchte controlegroep werden geen significante verschillen gevonden in intelligentie, performale intelligentie, verwerkingssnelheid, werkgeheugen, korte termijn geheugen, aandacht, gedrag en de structuur en functie van het hart. Echter, kinderen uit de kanker en zwangerschap groep en een subgroep van kinderen die aan chemotherapie werden blootgesteld hadden een lagere verbale intelligentie en visuo-spatiaal lange termijn geheugen, evenals een hogere diastolische bloeddruk. De uitkomsten van beide groepen lagen binnen de normaalwaarden. Daarnaast zagen we otoxiciteit bij drie kinderen die werden blootgesteld aan cisplatinum en hadden kinderen uit de kanker en zwangerschap groep een groter risico op het dragen van een bril. Verder waren we geïnteresseerd in de emotieregulatie van 37 kinderen die prenataal werden blootgesteld aan chemotherapie. Deze kinderen hadden meer moeite met het adequaat omgaan van emoties, gerapporteerd door hun ouders. Samenvattend vonden we dat deze kinderen op de leeftijd van zes jaar in vergelijking met de controlegroep een lagere verbale intelligentie hadden en meer moeite hadden met het reguleren van emoties. Aandacht voor de cognitieve en emotionele ontwikkeling van deze kinderen wordt geadviseerd. Ook wordt het opvolgen van het gehoor aanbevolen voor kinderen die prenataal aan cisplatinum zijn blootgesteld. In beide analyses was sprake van een heterogene studiegroep waarin alle soorten maternale maligniteiten werden geïncludeerd. In **Hoofdstuk 5** wordt daarom onderzocht wat het effect is van een hematologische maligniteit en behandeling tijdens de zwangerschap op de perinatale uitkomst, algehele gezondheid en neurocognitieve ontwikkeling van het kind. Prenatale blootstelling aan een hematologische maligniteit met of zonder behandeling had geen invloed op de neurocognitieve ontwikkeling van het kind op de lange termijn. We zagen wel dat de behoefte aan ondersteunende zorg in verband stond met het overlijden van moeder. Aandacht voor de emotionele ontwikkeling van deze kinderen wordt geadviseerd, met name voor de kinderen die hun moeder verloren.

Hoofdstuk 6 bespreekt de zeldzame tumor maagkanker tijdens de zwangerschap. In deze groep werden 8 van de 10 kinderen te vroeg geboren, veroorzaakt door pre-eclampsie, verslechtering van de conditie van moeder of therapie planning. Op één na overleden alle moeders binnen twee jaar na de bevalling. Van vier kinderen waren gegevens beschikbaar over de opvolging waarvan twee kinderen een hartonderzoek ondergingen waarbij geen afwijkingen werden gevonden. Eén kind met neonatale complicaties ontwikkelde cerebrale parese, epilepsie en hemianopsie. De complicaties vereisten intensieve fysiotherapie,

desondanks maakte het kind een normale cognitieve ontwikkeling door op 15 maanden, 3 jaar en 6 jaar. Een ander kind geboren met een zwangerschapsduur van 34 weken en 3 dagen kreeg een cognitief onderzoek op de leeftijd van 18 maanden en vertoonde een adequate cognitieve ontwikkeling voor de gecorrigeerde leeftijd voor de prematuriteit.

In **Hoofdstuk 7** wordt de impact van granulocyt-kolonie-stimulerende factor (G-CSF) bij dose-dense chemotherapie tijdens de zwangerschap besproken. In totaal werden 21 kinderen met een mediane opvolging van 18 maanden geïncludeerd in de klinische opvolging en daarbij werden geen neurologische of functionele hartafwijkingen gevonden. Bij vier kinderen was de motorische ontwikkeling vertraagd, waarvoor zij fysiotherapie kregen. Bij twee prematuur geboren kinderen werd een vertraagde cognitieve ontwikkeling gezien.

Richtlijnen voor neonatale en kindergeneeskundige zorg voor kinderen die zijn blootgesteld aan gynaecologische kankers tijdens de zwangerschap worden beschreven in **Hoofdstuk 8**. We adviseren langdurige opvolging van kinderen die prenataal zijn blootgesteld aan chemotherapie en behandeling in een specialistisch centrum met een multidisciplinair team zodat gynaecologen, oncologen, neonatologen en kinderartsen indien nodig betrokken worden bij de behandeling.

Appendices

Author contributions

List of publications

PhD portfolio

Curriculum Vitae

Dankwoord

AUTHOR CONTRIBUTIONS

Chapter 2. Management of cancer during pregnancy and current evidence of obstetric, neonatal and pediatric outcome: a review

Mathilde van Gerwen: study design and concepts, provision of study materials, collection and assembly of data, data analysis and interpretation, manuscript writing and final approval of manuscript. **Charlotte Maggen:** study design and concepts, provision of study materials, collection and assembly of data, data analysis and interpretation, manuscript writing and final approval of manuscript. **Kristel Van Calsteren:** study design and concepts and final approval of manuscript. **Tineke Vandenbroucke:** collection and assembly of data and final approval of manuscript. **Frédéric Amant:** study design and concepts, manuscript writing and final approval of manuscript.

Chapter 3. Association of chemotherapy timing in pregnancy with congenital malformation

Mathilde van Gerwen: study design and concepts, provision of patients, collection and assembly of data, data analysis and interpretation, manuscript writing and final approval of manuscript. **Charlotte Maggen:** study design and concepts, provision of patients, collection and assembly of data, data analysis and interpretation, manuscript writing and final approval of manuscript. **Elyce Cardonick:** provision of patients and final approval of manuscript. **Emma Verwaaijen:** data analysis and interpretation, manuscript writing and final approval of manuscript. **Marry van den Heuvel-Eibrink:** provision of patients, collection and assembly of data, and final approval of manuscript. **Roman G. Shmakov:** provision of patients and final approval of manuscript. Ingrid Boere: provision of patients and final approval of manuscript. **Mina M. Gziri:** provision of patients and final approval of manuscript. **Petronella B. Ottevanger:** provision of patients and final approval of manuscript. **Christianne Lok:** provision of patients and final approval of manuscript. **Michael Halaska:** provision of patients and final approval of manuscript. **Long Ting Shao:** provision of patients and final approval of manuscript. **Ilana Struys:** data analysis and interpretation, manuscript writing and final approval of manuscript. **Elisabeth M. van Dijk-Lokkart:** study design and concepts, data analysis and interpretation, manuscript writing and final approval of manuscript. **Kristel Van Calsteren:** study design and concepts, data analysis and interpretation, manuscript writing and final approval of manuscript. **Robert Fruscio:** provision of patients and final approval of manuscript. **Paolo Zola:** provision of patients and final approval of manuscript. **Giovanna Scarfone:** provision of patients and final approval of manuscript. **Frédéric Amant:** study design and concepts, data analysis and interpretation, manuscript writing and final approval of manuscript.

Chapter. 4 Pediatric outcome at age 6 after maternal cancer diagnosed during pregnancy

Child development at 6 years after maternal cancer diagnosis and treatment during pregnancy (original article and data article)

Mathilde van Gerwen: study design and concepts, provision of patients, collection and assembly of data, data analysis and interpretation, manuscript writing and final approval of manuscript. **Tineke Vandenbroucke:** study design and concepts, provision of patients, collection and assembly of data, data analysis and interpretation, manuscript writing and final approval of manuscript. **Magali Verheecke:** study design and concepts, provision of patients, collection and assembly of data, data analysis and interpretation, manuscript writing and final approval of manuscript. **Kristel Van Calsteren:** study design and concepts, provision of patients, data analysis and interpretation, manuscript writing and final approval of manuscript. **Michael Halaska:** provision of patients, manuscript writing and final approval of manuscript. **Monica Fumagalli:** provision of patients, manuscript writing and final approval of manuscript. **Robert Fruscio:** provision of patients, manuscript writing and final approval of manuscript. **Amarendra Gandhi:** data analysis and interpretation, manuscript writing and final approval of manuscript. **Margreet Veening:** provision of patients and final approval of manuscript. **Lieven Lagae:** provision of patients and final approval of manuscript. **Petronella B. Ottevanger:** provision of patients and final approval of manuscript. Jens-Uwe Voigt: provision of patients and final approval of manuscript. **Jorine de Haan:** provision of patients and final approval of manuscript. **Mina M. Gziri:** provision of patients and final approval of manuscript. **Charlotte Maggen:** provision of patients, manuscript writing and final approval of manuscript. **Luc Mertens:** provision of patients, collection and assembly of data, data analysis and interpretation, manuscript writing and final approval of manuscript. **Gunnar Naulaers:** provision of patients and final approval of manuscript. **Laurence Claes:** data analysis and interpretation, manuscript writing and final approval of manuscript. **Frédéric Amant:** study design and concepts, provision of patients, collection and assembly of data, data analysis and interpretation, manuscript writing and final approval of manuscript.

Executive functioning in 6 year old children exposed to chemotherapy in utero

Mathilde van Gerwen: study design and concepts, provision of patients, collection and assembly of data, data analysis and interpretation, manuscript writing and final approval of manuscript. **Tineke Vandenbroucke:** study design and concepts, provision of patients, collection and assembly of data, data analysis and interpretation and final approval of manuscript. **An-sofie Gorissen:** provision of patients and final approval of manuscript. **Martine van Grotel:** provision of patients and final approval of manuscript. **Marry van den Heuvel-Eibrink:** provision of patients and final approval of manuscript.

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Chapter 5. Long-term neurodevelopmental outcome after prenatal exposure to maternal hematological malignancies with or without cytotoxic treatment.

Mathilde van Gerwen: study design and concepts, provision of patients, collection and assembly of data, data analysis and interpretation, manuscript writing and final approval of manuscript. **Evangeline Huis in 't Veld:** provision of patients, collection and assembly of data, data analysis and interpretation, manuscript writing and final approval of manuscript. **Martine van Grotel:** provision of patients, manuscript writing and final approval of manuscript. **Marry van den Heuvel-Eibrink:** provision of patients, manuscript writing and final approval of manuscript. **Kristel Van Calsteren:** provision of patients, manuscript writing and final approval of manuscript. **Charlotte Maggen:** provision of patients, manuscript writing and final approval of manuscript. **Vit Drochytek:** provision of patients and final approval of manuscript. **Giovanna Scarfone:** provision of patients and final approval of manuscript. **Camilla Fontana:** provision of patients, manuscript writing and final approval of manuscript. **Robert Fruscio:** provision of patients, manuscript writing and final approval of manuscript. **Elyce Cardonick:** provision of patients, manuscript writing and final approval of manuscript. **Elisabeth M. van Dijk-Lokkart:** collection and assembly of data, data analysis and interpretation, manuscript writing and final approval of manuscript. **Frédéric Amant:** study design and concepts, provision of patients, collection and assembly of data, data analysis and interpretation, manuscript writing and final approval of manuscript.

Chapter 6. Gastric cancer during pregnancy: a report on 13 cases and review of the literature with focus on chemotherapy during pregnancy

Charlotte Maggen: study design and concepts, provision of patients, collection and assembly of data, data analysis and interpretation, manuscript writing and final approval of manuscript. **Christianne Lok:** study design and concepts, provision of patients, collection and assembly of data, data analysis and interpretation, manuscript writing and final approval of manuscript. **Elyce Cardonick:** provision of patients, manuscript writing and final approval of manuscript. **Mathilde van Gerwen:** provision of patients, collection and assembly of data, manuscript writing and final approval of manuscript.

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Chapter 7. Maternal and Neonatal Outcome after the Use of G-CSF for Cancer Treatment during Pregnancy

Claudia Berends: provision of patients, collection and assembly of data, data analysis and interpretation, manuscript writing and final approval of manuscript. **Charlotte Maggen:** provision of patients, collection and assembly of data, data analysis and interpretation, manuscript writing and final approval of manuscript. **Christianne Lok:** provision of patients, collection and assembly of data, data analysis and interpretation, manuscript writing and final approval of manuscript. **Mathilde van Gerwen:** provision of patients, collection and assembly of data, data analysis and interpretation, manuscript writing and final approval of manuscript. **Ingrid Boere:** provision of patients, manuscript writing and final approval of manuscript. Vera Wolters: provision of patients, manuscript writing and final approval of manuscript. **Kristel Van Calsteren:** study design and concepts, provision of patients, collection and assembly of data, manuscript writing and final approval of manuscript. **Heidi Segers:** data analysis and interpretation and final approval of manuscript. **Marry van den Heuvel-Eibrink:** provision of patients, manuscript writing and final approval of manuscript. **Rebecca Painter:** provision of patients, manuscript writing and final approval of manuscript. **Mina M. Gziri:** provision of patients, manuscript writing and final approval of manuscript. **Frédéric Amant:** study design and concepts, provision of patients, collection and assembly of data, data analysis and interpretation, manuscript writing and final approval of manuscript.

Chapter 8. Gynecologic cancers in pregnancy: guidelines based on a third international consensus meeting

Frédéric Amant, Paul Berveiller, Ingrid Boere, Elyce Cardonick, Robert Fruscio, Monica Fumagalli, Michael Halaska, Annette Hasenburg, Anna Johansson, Matteo Lambertini, Christianne Lok, Charlotte Maggen, Philippe Morice, Fedro Peccatori, Philip Poortmans, Kristel Van Calsteren, Tineke Vandenbroucke,

Mathilde van Gerwen, Marry van den Heuvel-Eibrink, Flora Zagouri and **Ignacio Zapardiel,** all members of the International Network on Cancer, Infertility and Pregnancy (INCIP), were selected based on their expertise. Fields that were covered include oncology, medical oncology, clinical pharmacology, obstetrics, pediatrics, psychology and radiation oncology. All participants were assigned to draft a section on the topic of their experience. All the sections were merged into a new manuscript, which was remotely discussed two times. The final version served as the basis for the discussion during the meeting, which took place in Madrid on the 23rd December 2018. Discussions during the meeting resulted in a new version that circulated two times. All participants agreed with the final recommendations.

LIST OF PUBLICATIONS

Publications in this thesis

Management of cancer during pregnancy and current evidence of obstetric, neonatal and pediatric outcome: a review article
van Gerwen M*, Maggen C*, Van Calsteren K, Vandenbroucke T, Amant F.
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Association of chemotherapy timing in pregnancy with congenital malformation
van Gerwen M*, Maggen C*, Cardonick E, Verwaaijen E, van den Heuvel-Eibrink M, Shmakov RG, Boere I, Gziri MM, Ottevanger PB, Lok CAR, Halaska MJ, Shao LT, Struys I, van Dijk-Lokkart EM, Van Calsteren K, Fruscio R, Zola P, Scarfone G, Amant F.
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van Gerwen M*, Vandenbroucke T*, Verheecke M*, Van Calsteren K, Halaska MJ, Fumagalli M, Fruscio R, Gandhi A, Veening M, Lagae L, Ottevanger PB, Voigt JU, de Haan J, Gziri MM, Maggen C, Mertens L, Naulaers G, Claes L, Amant F.
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Data describing child development at 6 years after maternal cancer diagnosis and treatment during pregnancy
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Executive functioning in 6 year old children exposed to chemotherapy in utero
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van Gerwen M, Huis In 't Veld E, van Grotel M, van den Heuvel-Eibrink M, Van Calsteren K, Maggen C, Drochytek V, Scarfone G, Fontana C, Fruscio R, Cardonick E, van Dijk-Lokkart EM, Amant F.
Child Neuropsychol. 2021 Apr;20:1-12.

A report on 13 cases and review of the literature with focus on chemotherapy during pregnancy
Maggen C, Lok CAR, Cardonick E, **van Gerwen M**, Ottevanger PB, Boere IA, Koskas M, Halaska MJ, Fruscio R, Gziri MM, Witteveen PO, Van Calsteren K, Amant F.
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Maternal and Neonatal Outcome after the Use of G-CSF for Cancer Treatment during Pregnancy
Berends C*, Maggen C*, Lok CAR, **van Gerwen M**, Boere IA, Wolters VERA, Van Calsteren K, Segers H, van den Heuvel-Eibrink M, Painter RC, Gziri MM, Amant F.
Cancers. 2021 Mar;13(6):1214.

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Amant F, Berveiller P, Boere IA, Cardonick E, Fruscio R, Fumagalli M, Halaska MJ, Hasenburg A, Johansson ALV, Lambertini M, Lok CAR, Maggen C, Morice P, Peccatori F, Poortmans P, Van Calsteren K, Vandenbroucke T, **van Gerwen M**, van den Heuvel-Eibrink M, Zagouri F, Zapardiel I.
Ann Oncol. 2019 Oct;30(10):1601-1612.

Publications related to this thesis

Long-Term Neurodevelopmental Outcome of Children after in Utero Exposure to Chemotherapy
Korakiti AM, Zografos E, **van Gerwen M**, Amant F, Dimopoulos MA, Zagouri F.
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EClinicalMedicine. 2020 Oct;28:100598.

Severe Adverse Reaction to Vemurafenib in a Pregnant Woman with Metastatic Melanoma de Haan J, van Thienen JV, Casaer M, Hannivoort RA, Van Calsteren K, van Tuyl M, **van Gerwen M**, Debeer A, Amant F, Painter RC.
Case Rep Oncol. 2018 Feb;11(1):119-124.

**These authors contributed equally*

PHD PORTFOLIO

PhD candidate	M.M.A. van Gerwen
PhD period	May 2017 – May 2021
Promotor	Prof. dr. F.C.H. Amant
Copromotor	dr. E.M. van Dijk-Lokkart

PhD Training

General courses	***Year***	***ECTS***
Basis course for clinical investigators (BROK) *Netherlands Cancer Institute, Amsterdam, the Netherlands*	2017	1
Writing a scientific paper *Netherlands Cancer Institute, Amsterdam, the Netherlands*	2018	2
Basic medical statistics *Netherlands Cancer Institute, Amsterdam, the Netherlands*	2019	1.5
Specific courses	***Year***	***ECTS***
Emotional wellbeing in the peripartum period *University Psychiatric Center KU Leuven, Leuven, Belgium*	2017	0.25
Maternal medicine: multi-disciplinary approach of pregnancy complications *Boerhaave Medical Education, Leiden, the Netherlands*	2019	0.5
Seminars, workshops and master classes	***Year***	***ECTS***
How to become a successful grant applicant *Netherlands Cancer Institute, Amsterdam, the Netherlands*	2018	0.05
Getting your manuscript out *VU Medical Center, Amsterdam, the Netherlands*	2018	0.4
PhD Day *Netherlands Cancer Institute, Amsterdam, the Netherlands*	2018	0.25
The teenage brain *VU University, Amsterdam, the Netherlands*	2018	0.25
Hackathon *Netherlands Cancer Institute, Amsterdam, the Netherlands*	2019	0.25
Fundamentals of intelligence *Pearson Academy, Amsterdam, the Netherlands*	2019	0.25
Seminar and lunch with Puck Knipscheer *Netherlands Cancer Institute, Amsterdam, the Netherlands*	2019	0.1

Symposium Adviesgroep Kanker en Zwangerschap *Netherlands Cancer Institute, Amsterdam, the Netherlands*	2019	0.25
Presentations	***Year***	***ECTS***
Neuropsychological outcome after cancer treatment in utero *Symposium AKZ, IKNL, Utrecht, the Netherlands, oral presentation*	2017	0.5
Pediatric outcome after Maternal Cancer Diagnosed during pregnancy *OOA retreat, Renesse, the Netherlands, poster presentation*	2017	0.5
Follow-up of children exposed to maternal cancer (treatment) in pregnancy *INCIP meeting, Warsaw, Poland, virtual, oral presentation*	2018	0.5
Follow-up of children exposed to maternal cancer and treatment during pregnancy *Symposium, AMC, Amsterdam, the Netherlands, oral presentation*	2018	0.5
Emotional wellbeing of pregnant women with cancer and their relatives *INCIP scientific meeting, Madrid, Spain, oral presentation*	2019	0.5
Follow-up of children exposed to maternal cancer and treatment during pregnancy *INCIP scientific meeting, Madrid, Spain, workshop*	2019	0.5
Long term outcome of children after in-utero exposure *Conference on Cancer In Pregnancy (15 years after), Milan, Italy, oral presentation*	2019	0.5
Surveillance of children prenatally exposed to maternal malignancy and cancer treatment *Scientific meeting of Alvaro Cabrera Garcia, Mexico, virtual, oral presentation*	2019	0.5
Neurocognitive outcome after maternal cancer and treatment in utero *Scientific meeting of Child & Adolescent Psychiatry and Psychosocial Care, Amsterdam UMC, the Netherlands, virtual, oral presentation*	2020	0.5
Cancer In Pregnancy *Meeting of Ingeborg Douwes Centrum, Amsterdam, the Netherlands, virtual, oral presentation*	2021	0.5

(Inter)national conferences and scientific meetings	*Year*	*ECTS*
European Conference on Developmental Psychology *Utrecht, the Netherlands*	2017	0.5
Annual Retreat Oncology Graduate School (OOA) *Renesse, the Netherlands*	2017	1.5
European Pediatric Psychology Conference *Ghent, Belgium*	2018	0.5
Consensus Meeting Gynecologic Cancers during Pregnancy *Madrid, Spain*	2019	0.25
Scientific Meeting of International Network on Cancer, Infertility and Pregnancy *Madrid, Spain*	2019	0.5
Cancer In Pregnancy (15 years after) *Milan, Italy*	2019	0.5
Symposium Pediatric Psychology *Utrecht, the Netherlands*	2019	0.25
Retreat van den Heuvel-Eibrink Group *Schiermonnikoog, the Netherlands and Virtual Edition*	2019-2020	2
Scientific Meeting of International Network on Cancer, Infertility and Pregnancy *Virtual Edition*	2020	0.5
Meeting of Posmat project group *Virtual*	2020	0.25
Other	***Year***	***ECTS***
Weekly research meeting of the Cancer in Pregnancy Research Group	2017-2021	7
Weekly research meeting van den Heuvel-Eibrink Research Group	2020-2021	3

Teaching

Lecturing	*Year*	*ECTS*
Lecture long-term follow of children exposed to chemotherapy *Princess Máxima Center, Utrecht, the Netherlands*	2019	1

Parameters of Esteem

Grants	*Year*
Stichting Mitialto Budget: €5.000	2018
KWF Dutch Cancer Society Cancer treatment during pregnancy: addressing the later concerns of its fetal safety (CRADLE-II) Budget: €474.000	2021

CURRICULUM VITAE

Mathilde van Gerwen was born on June 12, 1991 in the city of Den Bosch in the Netherlands. She grew up in Eindhoven and attended secondary school at the Van Maerlantlyceum in Eindhoven. After her graduation in 2010, she went on to study Health Sciences with a specialization in Mental Health at Maastricht University. After receiving her Bachelor of Science degree in Health Sciences she earned a Master of Science degree in Neuropsychology and a Master of Science degree in Mental Health Sciences. During her Master studies she completed a clinical and a research internship at the department of Psychiatry and Psychology of the Maastricht University Medical Center.

In October 2015, she started work as a neuropsychologist at the Brain & Learning Center at the VU Amsterdam. In May 2017, she became a PhD candidate at the center for Gynecological Oncology Amsterdam at the Antoni van Leeuwenhoek - Netherlands Cancer Institute and VU Medical Center under the supervision of prof. dr. Frederic Amant and dr. Alice van Dijk-Lokkart. She performed a cohort study of Dutch children exposed to antenatal cancer and cancer treatment. She focused on whether children who were prenatally exposed to maternal malignancy and its treatment are at risk of long-term developmental problems with a major focus on the neurocognitive development. Mathilde also became a member of the International Network on Cancer in Pregnancy. In 2018, the follow-up for the Dutch children was nationally centralized in the Princess Máxima Center for pediatric oncology in Utrecht. Under the supervision of prof. dr. Marry van den Heuvel-Eibrink and dr. Martine van Grotel, she established an expertise outpatient clinic named 'Cancer In Pregnancy outpatient clinic'. On top of that, she facilitated the establishment of a patient support organization founded by the mother from one of the children in the Dutch follow-up cohort. Next to finishing her PhD trajectory, she is currently employed as a part-time psychologist at the department of child and adolescent psychiatry and psychosocial care of the Amsterdam University Medical Center.

DANKWOORD

Het voelt een beetje dubbel. Na vier jaar onderzoek sluit ik een belangrijke periode in mijn leven af maar daar staat wel tegenover dat ik een bijdrage heb mogen leveren aan een heel bijzonder en uniek onderzoek. Ik heb zowel in nationaal als internationaal verband met veel ziekenhuizen en teams mogen werken. Met dit dankwoord wil ik daarom eenieder bedanken die heeft bijgedragen aan dit onderzoek en graag maak ik van de gelegenheid gebruik om een aantal mensen in het bijzonder te bedanken.

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Marry, je hebt het onderzoek naar een hoger niveau getild. Je faciliteerde een polikliniek voor mijn onderzoekspopulatie en dit was de belangrijkste mijlpaal van mijn onderzoek. Je gaf me unieke kansen. Ik heb ontzettend veel waardering voor je. Martine, vanaf het eerste moment droeg je veel zorg voor onze nieuwe polikliniek. Je sprak altijd je bewondering uit en was ontzettend betrokken. Een flauwe Brabantse grap mocht ook niet ontbreken en Da ge bedankt zijt da witte.

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Beste Marie, Katrien, Jorine, Indra, Kaat, Cettina, Lara, Jeroen, Ilana, Hanne en Liesbeth. Jullie doen bijzonder mooi werk. Het is bijzonder hoe we met verschillende achtergronden en nationaliteiten op deze manier samenwerken. Ik weet dat jullie soms

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Ik ben een veel gebruiker van de intercity met traject Maastricht – Eindhoven – Den Bosch – Utrecht maar met zo'n gezellige familie in het Brabantse land en schoonfamilie in Maastricht kan dat ook niet anders. Lieve Anne en Fleur, gelukkig soms ook gewoon op de fiets of met de benenwagen in het Utrechtse. Mart, bedankt voor het mooie ontwerp voor mijn proefschrift. Ik bewonder je creativiteit en nauwkeurigheid.

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Iemand vroeg mij ooit: waarom zeg jij altijd tante Marga? Allereerst vond ik dit een gekke vraag maar daarna dacht ik het is inderdaad bijzonder dat ik jou altijd aanspreek met de verwijzing naar onze relatie. Maar je bent ook niet zomaar een tante. Een tante, een tweede moeder en iemand die mij leerde om je ambities na te streven. Bedankt voor al je vertrouwen en jouw gave om mij altijd van alle actualiteiten te voorzien.

Lieve mama, bedankt voor degene die jij bent. De hoeveelheid telefoontjes en appjes tussen ons zijn oneindig. Je betrokkenheid en mensenkennis zijn buitengewoon. Je vindt alles wat ik doe fantastisch maar je bent ook kritisch. Bij jou kan ik altijd zijn wie ik wil zijn en ik ben dan ook heel blij dat jij mijn mama bent.

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