KU Leuven
Biomedical Sciences Group
Faculty of Medicine
Department of Oncology

DOCTORAL SCHOOL
BIOMEDICAL SCIENCES

VRIJE
UNIVERSITEIT
AMSTERDAM

THE IMPACT OF AN INTERNATIONAL ADVISORY BOARD ON THE MANAGEMENT OF CANCER DURING PREGNANCY

Improving clinical care and tackling exceptional situations

Joosje Heleen Heimovaara

Jury:

Supervisor KU Leuven:	Prof. dr. Frédéric Amant
Supervisor VU Amsterdam:	Prof. dr. Lia van Zuylen
Co-supervisor(s):	Prof. dr. Kristel Van Calsteren (KU Leuven)
	Dr. Christianne Lok (NKI-AVL/VU Amsterdam)
Chair examining committee:	Prof. Ronny Bruffaerts
Chair public defence:	Prof. Baki Topal
Jury members:	Prof. dr. Hans Wildiers (KU Leuven)
	Prof. dr. Liesbeth Lewi (KU Leuven)
	Prof. dr. Philip Poortmans (University of Antwerp)
	Dr. Tineke Buffart (VU Amsterdam)
	Dr. Inge Baas (UMC Utrecht)

Dissertation presented in partial fulfilment of the requirements for the joint/double degree of Doctor of Biomedical sciences (KU Leuven) and Doctor of Philosophy (VU Amsterdam)

Leuven, 2024

Copyright © 2024 Joosje Heimovaara

All rights reserved. No part of this thesis may be reproduced, stored in a retrieval system, or transmitted in any form or by any means, electronic, mechanical, photocopying, recording or otherwise without permission of the author.

Table of contents

Part I Introduction 4

Chapter 1 General introduction 5

Chapter 2 Management of pregnancy in women with cancer 11

Chapter 3 Objectives and outline of this thesis 29

Part II Pooling knowledge: an Advisory Board for Cancer, Infertility and Pregnancy 31

Chapter 4 Results of an international survey on the current organization of care for pregnant women with cancer 32

Chapter 5 Ten-year experience of a national multidisciplinary tumour board for cancer and pregnancy in the Netherlands 42

Chapter 6 The Advisory Board on Cancer, Infertility and Pregnancy: a virtual on-demand multidisciplinary tumour board 58

Part III Clinical challenges in the field of Cancer in Pregnancy 61

Chapter 7 Maternal death by cancer in pregnancy: A descriptive study of the International Network on Cancer, Infertility and Pregnancy 62

Chapter 8 Obstetric and oncological outcomes of patients diagnosed with sarcoma during pregnancy: A report on cases from the INCIP and review of literature 76

Chapter 9 Guidelines on diagnosis and treatment of hematological malignancies during pregnancy 88

Chapter 10 Immunotherapy for cancer treatment during pregnancy 116

Chapter 11 Severe immune-related enteritis after in utero exposure to pembrolizumab. 138

Chapter 12 Proton therapy of a pregnant patient with nasopharyngeal carcinoma – a case-report 149

Part IV General discussion and conclusion 157

Appendices 170

Scientific summary 171

Samenvatting 174

List of abbreviations 177

Supplementary appendix 179

Scientific acknowledgements, personal contribution, conflicts of interest and AI statement 195

Curriculum Vitae 199

List of publications 201

Dankwoord 203

Part I Introduction

Chapter 1 General introduction

CANCER IN PREGNANCY

Cancer in pregnancy is a rare occurrence, yet it affects over 200,000 pregnant women worldwide each year.[1] With the increasing availability of data on common tumours in pregnancy, it has become evident that most imaging modalities are safe for use during pregnancy and many chemotherapeutic agents can be administered from the second trimester onwards.[2-4] It is generally recommended that oncological treatment for pregnant women should align as closely as possible with treatments in non-pregnant women to ensure the best maternal prognosis.

Most oncologists in Europe will see a pregnant woman with cancer only once every five years.[5] As a result, many physicians lack the expertise and confidence to diagnose and treat pregnant women with cancer according to the most recent insights, which can lead to suboptimal oncological and obstetric care.[6] Up-to-date insights are important as novel treatment options such as immunotherapy, targeted therapy or proton therapy are increasingly being used in young (non-pregnant) women with cancer. This raises questions about the safety of their use during pregnancy. Unfortunately, physicians currently have to base their treatment plans with regard to these novel agents mainly on what is known from case reports or case series in the literature. Therefore, physicians may find it difficult to manage these situations and can be hesitant about how to provide the best care for these women.

LEVELS OF EVIDENCE: CHALLENGES IN CANCER IN PREGNANCY

In evidence-based medicine (EBM), the standard approach in healthcare nowadays, higher levels of evidence are aimed for to achieve more reliable, objective, and generalizable data for clinical decision-making. The EBM pyramid ranks evidence based on methodological rigor and susceptibility to bias, with randomized controlled trials (RCTs) and systematic reviews of RCTs (level 1 evidence) at the top and case studies (level 4 evidence) almost at the bottom (Figure 1).[7] The higher-level evidence minimizes biases like selection and confounding. The randomization process ensures that patient characteristics are balanced between treatment and control groups, allowing for a clearer assessment of treatment effects.

Medical research begins with careful observation and the development of theoretical frameworks. The strength of evidence from a clinical study is directly linked to how well bias and variability were controlled during the study, as well as the significance of the observed effect. This is already pointed out in the EBM pyramid. Clinical studies are broadly categorized as uncontrolled observations, observational comparisons, and controlled clinical trials.

However, the management of cancer in pregnancy is solely based on case series and retrospective studies. Case series and cohort studies represent levels 2 to 4 evidence according to the EBM pyramid. High-level evidence is lacking because prospective, randomized trials are not feasible from ethical point of view. So, clinical guidelines based on systematic reviews and RCTs are not possible in this patient population.

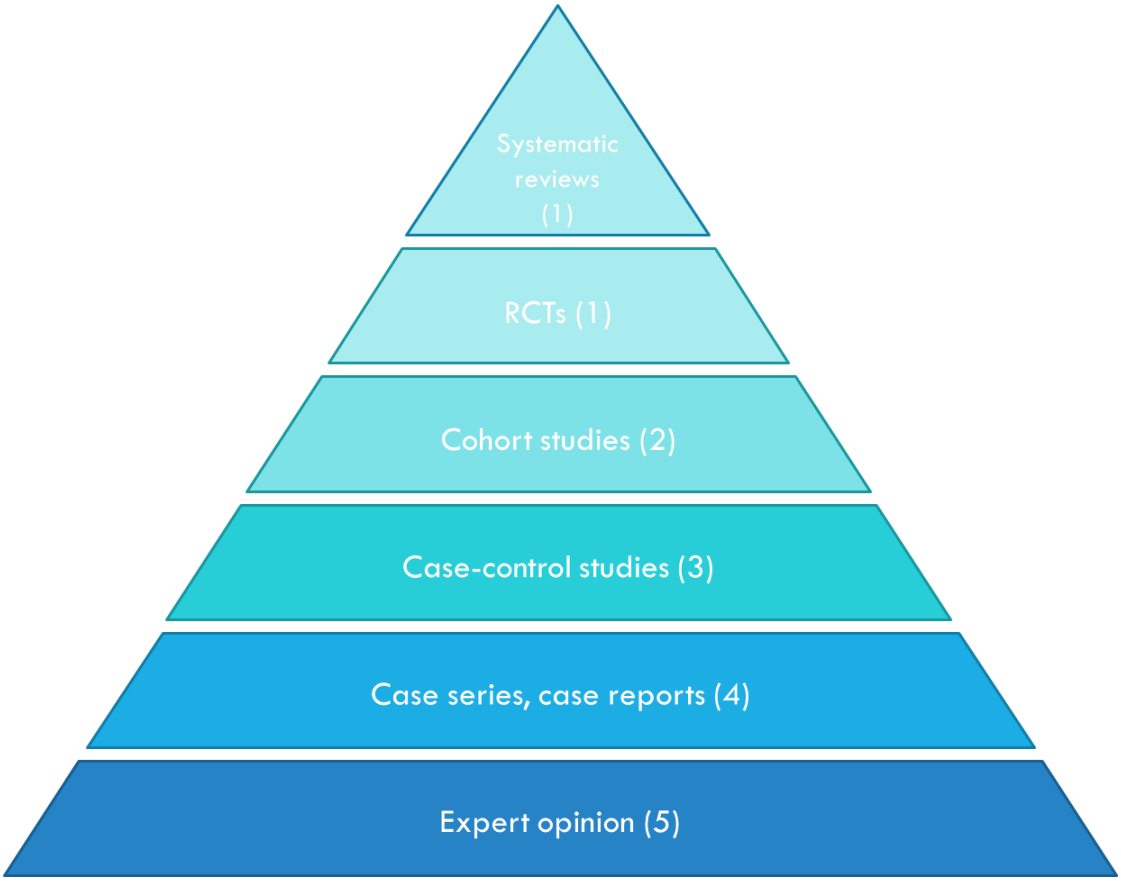


Figure 1. EBM levels of evidence pyramid. According to the EBM levels of evidence pyramid, the quality of evidence increases and the risk of bias decreases with increasing levels of the pyramid.

In the context of cancer in pregnancy, the lack of high-level evidence means that treatment decisions are often guided by individual clinical decision-making, multidisciplinary input, and available case-based data. This also highlights the importance of collecting and sharing real-world evidence through registries and collaborative cohort studies, which can provide valuable insights over time. Although level 2 to 4 evidence may not provide the same robustness as randomized trials, it is the best available data in rare and ethically complex cases, and it plays a crucial role in informing practice and ensuring that pregnant women with cancer receive appropriate care.

INCIP: FROM CASE REPORT TO COHORT STUDY

Inspired by a very determined pregnant woman with cervical cancer who wished to preserve her pregnancy, a “Cancer in Pregnancy” task force was established at the University Hospital of Leuven under

the umbrella of the European Society of Gynaecological Oncology (ESGO) in 2005.[8] At the time, the literature consisted of only a handful case reports or small case series (level 4 evidence). Professor Amant started a registry combining oncological and obstetrical data, first only in Belgium, and later expanded to an international registry. In 2014, the *International Network of Cancer, Infertility and Pregnancy* (INCIP, www.cancerinpregnancy.org) was established, for pregnant women diagnosed with cancer and for women undergoing fertility preservation before cancer treatment.[8] As of February 2024, INCIP had registered 2956 women with a cancer diagnosis during pregnancy, with the distribution of malignancies registered shown in Figure 2.

The INCIP registry study is a cohort study focussing on the oncological and obstetrical outcomes of women exposed to cancer(treatment) during pregnancy and on the long-term follow up of their children. The study was initiated to obtain evidence on the safety and efficacy of oncological treatment during pregnancy. [6,9-14] Knowledge based on the collected data already led to the development of guidelines for the management of the most common tumour types in pregnant women.[15-17] Although the INCIP registry should be scientifically characterised as level 2 to 4 evidence, it allows for long-term cohort studies and also collects case descriptions for rarer tumour types that can lead to new insights with regard to treatment options.

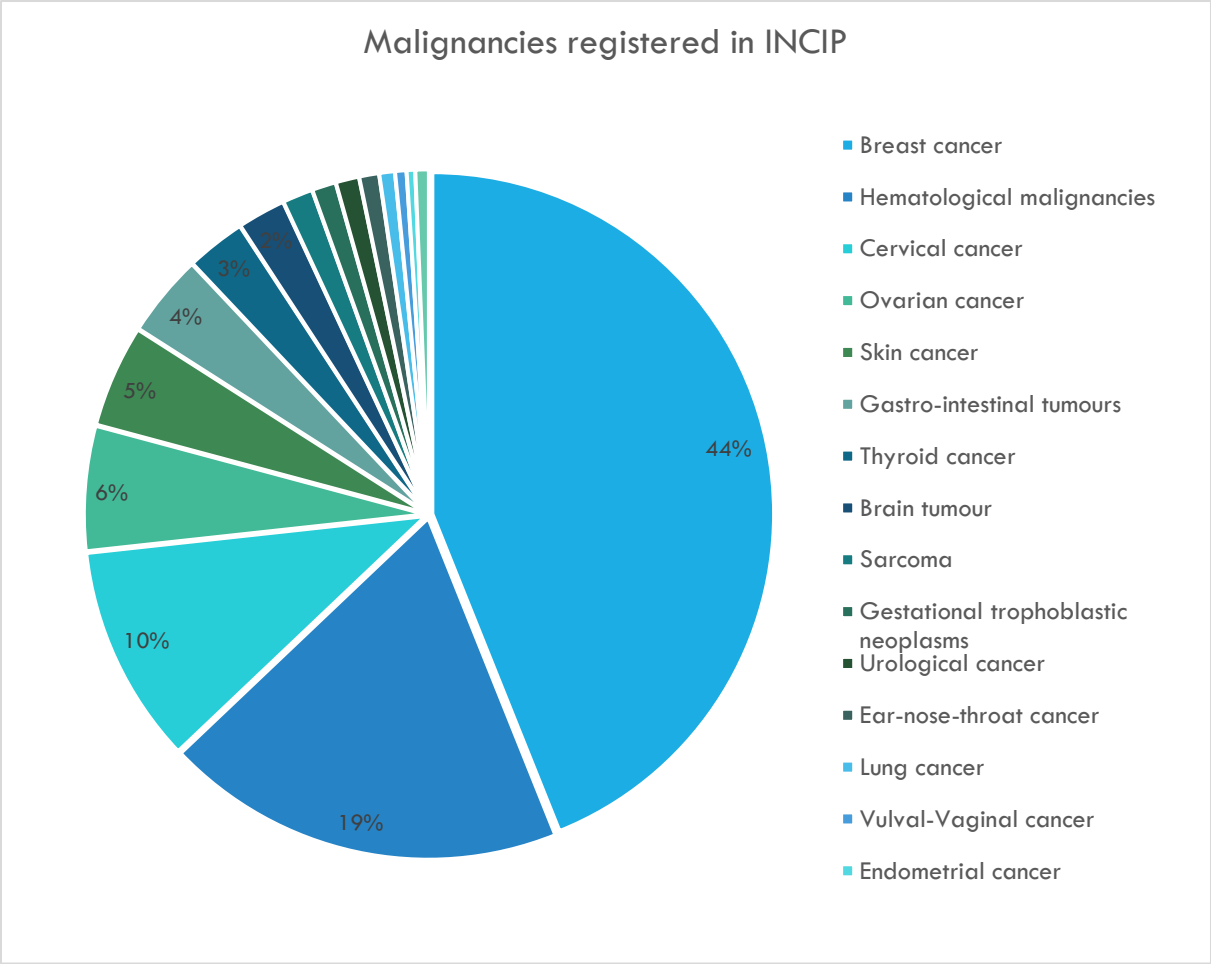


Figure 2. Overview of malignancies registered in the INCIP database in September 2024

MULTIDISCIPLINARY ADVISORY BOARDS: THE IMPORTANCE OF COLLABORATION

When deciding on diagnostics and treatment on an individual patient level, multidisciplinary tumour boards are considered standard of care in the oncological field. It ensures that patients are treated according to the best treatment available and that consensus can be reached when high level-evidence is lacking.[18-20] For the management of women with cancer in pregnancy, establishment of specialized multidisciplinary boards in every hospital is not feasible. Next to that, geographical and logistical barriers can make it difficult to refer all patients to specialised hospitals. Finding alternative ways to provide the most optimal multidisciplinary care for these patients is therefore of great importance.

In response to this need, the Dutch national multidisciplinary advisory board **(**MDAB) on cancer in pregnancy, '*Adviesgroep Kanker en Zwangerschap*', was established in 2012. This digital MDAB was created to support physicians in making treatment decisions for their pregnant patients with cancer. In this MDAB, Dutch physicians working in different hospitals spread all over the Netherlands, with diverse medical backgrounds including various oncological sub-disciplines, as well as fertility, obstet-

rics, paediatrics and ethical care, will discuss the questions formulated by the patient's treating physician. Subsequently, a collective advice is sent. Since its establishment up until September 2024, the Dutch MDAB has received over 400 advice requests from more than 100 physicians in the Netherlands.

With the national success of the Dutch MDAB, a growing amount of advice requests came from abroad. Following this call, the initiative was taken to establish a similar international MDAB to discuss the management of pregnant patients with cancer within the INCIP network, the '*Advisory Board on Cancer, Infertility and Pregnancy (ABCIP)'*. ABCIP will allow to disseminate knowledge based on the INCIP database, and improve maternal and fetal care.[6,8]

REFERENCES

1 Han, S. N. *et al.* Cancer in pregnancy: a survey of current clinical practice. *Eur J Obstet Gynecol Reprod Biol* **167**, 18-23 (2013).

2 Vandecaveye, V., Amant, F., Lecouvet, F., Van Calsteren, K. & Dresen, R. C. Imaging modalities in pregnant cancer patients. *International journal of gynecological cancer : official journal of the International Gynecological Cancer Society* **31**, 423-431 (2021).

3 van Gerwen, M. *et al.* Association of Chemotherapy Timing in Pregnancy With Congenital Malformation. *JAMA Netw Open* **4**, e2113180 (2021).

4 Maggen, C., Van Gerwen, M., Van Calsteren, K., Vandenbroucke, T. & Amant, F. Management of cancer during pregnancy and current evidence of obstetric, neonatal and pediatric outcome: A review article. *International Journal of Gynecological Cancer* **29**, 404-416 (2019).

5 Lok, C. & Amant, F. Editorial: The challenge of treating and investigating rare gynaecologic cancers. *Curr Opin Oncol* **33**, 432-434 (2021).

6 de Haan, J. *et al.* Oncological management and obstetric and neonatal outcomes for women diagnosed with cancer during pregnancy: a 20-year international cohort study of 1170 patients. *The Lancet Oncology* **19**, 337-346 (2018).

7 *OCEBM Levels of Evidence Working Group. "The Oxford Levels of Evidence 2". Oxford Centre for Evidence-Based Medicine. https://www.cebm.ox.ac.uk/resources/levels-of-evidence/ocebm-levels-of-evidence*.

8 Maggen, C. *et al.* Pregnancy and Cancer: the INCIP Project. *Current Oncology Reports* **22** (2020).

9 Amant, F. *et al.* Pediatric outcome after maternal cancer diagnosed during pregnancy. *New England Journal of Medicine* **373**, 1824-1834 (2015).

10 van Gerwen, M. *et al.* Long-term neurodevelopmental outcome after prenatal exposure to maternal hematological malignancies with or without cytotoxic treatment. *Child Neuropsychol* **27**, 822-833 (2021).

11 Vandenbroucke, T. *et al.* Psychological distress and cognitive coping in pregnant women diagnosed with cancer and their partners. *Psycho-Oncology* (2017).

12 Blommaert, J. *et al.* The impact of cancer and chemotherapy during pregnancy on child neurodevelopment: A multimodal neuroimaging analysis. *EClinicalMedicine* **28**, 100598 (2020).

13 Blommaert, J. *et al.* Long-term impact of prenatal exposure to chemotherapy on executive functioning: An ERP study. *Clinical Neurophysiology* **130**, 1655-1664 (2019).

14 Vandenbroucke, T. *et al.* Child development at 6 years after maternal cancer diagnosis and treatment during pregnancy. *Eur J Cancer* **138**, 57-67 (2020).

15 Loibl, S. *et al.* Breast Cancer Diagnosed During Pregnancy: Adapting Recent Advances in Breast Cancer Care for Pregnant Patients. *JAMA Oncol* **1**, 1145-1153 (2015).

16 Lishner, M. *et al.* Hematologic malignancies in pregnancy: Management guidelines from an international consensus meeting. *Journal of Clinical Oncology* **34**, 501-508 (2016).

17 Amant, F. *et al.* Gynecologic cancers in pregnancy: Guidelines based on a third international consensus meeting. *Annals of Oncology* **30**, 1601-1612 (2019).

18 Thenappan, A. *et al.* Review at a multidisciplinary tumor board impacts critical management decisions of pediatric patients with cancer. *Pediatric Blood \& Cancer* **64 (2)**, 254-258 (2017).
19 Wright, F. C., De Vito, C., Langer, B. & Hunter, A. Multidisciplinary cancer conferences: A systematic review and development of practice standards. *European Journal of Cancer* (2007).
20 Petty, J. K. & Vetto, J. T. Beyond doughnuts: tumor board recommendations influence patient care. *J Cancer Educ* **17**, 97-100 (2002).

Chapter 2 Management of pregnancy in women with cancer

Vera Wolters, **Joosje Heimovaara,** Charlotte Maggen, Elyce Cardonick, Ingrid Boere, Liesbeth Lenaerts, Frédéric Amant

International Journal of Gynaecological Cancer, March 2021

ABSTRACT

As the incidence of cancer in pregnancy has been increasing in recent decades, more specialists are confronted with a complex oncologic-obstetric decision-making process. With the establishment of (inter)national registries, including the International Network on Cancer, Infertility and Pregnancy, and an increasing number of smaller cohort studies, more evidence on the management of cancer during pregnancy is available. As fetal, neonatal and short-term pediatric outcomes after cancer treatment are reassuring, more women receive treatment during pregnancy. Prenatal treatment should adhere to standard treatment as much as possible to optimize maternal prognosis, always taking into account fetal wellbeing.

In order to guarantee the optimal treatment for both mother and child, a multidisciplinary team of specialists with expertise should be involved. Apart from oncologic treatment, a well-considered obstetric and perinatal management plan discussed with the future parents is crucial. Results of non-invasive prenatal testing are inconclusive in women with cancer and alternatives for prenatal anomaly screening should be used. Especially in women treated with chemotherapy, serial ultrasounds are strongly recommended to follow up fetal growth and cervical length. After birth, a neonatal assessment allows the identification of any cancer or treatment-related adverse events. In addition, placental histologic examination aims to assess the fetal risk of metastasis, especially in women with malignant melanoma or metastatic disease. Breastfeeding is discouraged when systemic treatment needs to be continued after birth. At least a three-week interval between the last treatment and nursing is recommended to prevent any treatment-induced neonatal effects from most non-platinum chemotherapeutic agents.

INTRODUCTION

Approximately 1 in 2000 pregnancies is complicated by cancer and the incidence has been increasing in recent decades.[1] In countries where women still tend to postpone childbirth to a later age for socio-economic reasons, the incidence of cancer in pregnancy will continue to increase. The implementation of non-invasive prenatal testing, which has the ability to detect preclinical cancer, is expected to further contribute to this increase.[2] Breast cancer, cervical cancer and melanoma are the most frequently occurring cancers in pregnancy.[3]

Oncologic management during pregnancy should be multidisciplinary, however, this continues to be a challenge. If there is a desire to preserve the pregnancy, specialists need to weigh maternal and fetal wellbeing and opt for the optimal oncologic treatment without significantly endangering fetal and maternal safety. In general, oncologic treatment in pregnancy should adhere to treatments used for non-pregnant patients as much as possible to conserve maternal prognosis. Besides surgery, systemic treatment, if compatible with pregnancy, plays an important role in antenatal oncologic treatment. Termination of pregnancy can be considered in the case of an aggressive or advanced stage cancer in early pregnancy. Preterm induction of delivery in order to start oncologic treatment should be avoided where possible because of long-term morbidities of preterm children.[4]

As awareness about this complex coincidence has been increasing, research has expanded to large-scale registries.[5] Overall, obstetric outcome has improved in the recent decades, with fewer terminations of pregnancy and fewer preterm deliveries.[5] Changes in obstetric management have been driven by an increased knowledge of cancer in pregnancy and an overall tendency to reduce medicalization. A recent Italian monocentric study has observed a trend towards fewer elective cesareans in the last decade.[6] This was accompanied by an increasing percentage of inductions of labor, mainly on account of the need to start or continue chemotherapy treatment.[6] Neonatal outcome in terms of cognitive and cardiac development in the first six years after chemotherapy exposure is not significantly affected in comparison with children in the general population.[4,7] Certain precautions are required as chemotherapy during pregnancy is associated with fetal growth impairment and, when administered early in pregnancy, congenital malformations.[5]

Current research mainly focused on the feasibility and safety of oncologic treatment in women with cancer. However, reports with an obstetric point of view on this topic are scarce. Here, we describe the different aspects of obstetric and perinatal management of women with cancer and discuss fetal and neonatal effects of cancer diagnostics and treatment.

EFFECTS OF DIAGNOSTICS ON THE DEVELOPING FETUS

Ionizing diagnostic imaging should be minimized during pregnancy due to the teratogenicity of radiation.[8] Although commonly used doses are often much lower than the threshold for dose-dependent side-effects of ionizing radiation (deterministic effects), exposures above this threshold have been associated with fetal death, mental retardation, malformations and growth disturbances.[9] The risk of stochastic carcinogenic effects of radiation depends on the gestational age during imaging and have been shown to rise with increasing dose. It is recommended that only examinations with a potential effect on the oncologic management are performed. The cumulative fetal dose of radiation should not exceed 100mGy.[8] The lifetime attributed cancer incidence for a radiation dose of 50 mGy is roughly estimated at 2% if the fetus is exposed after 15 weeks of gestation, but accurate quantification is impossible.[10] In recent decades, ionizing techniques have improved and fetal radiation doses have declined. Fetal radiation exposure should be discussed with an expert radiologist and a medical physicist should conduct an a priori estimation of the fetal dose level for each pregnant individual.

Non-ionizing imaging procedures, such as ultrasound and magnetic resonance imaging (MRI) are safe techniques for staging in pregnant patients. As the fetal effects are unclear, it is recommended to administer gadolinium, a MRI contrast product, with caution to pregnant patients, outweighing the diagnostic benefit and potential fetal risks.[11]

In non-pregnant patients, fluorine-18-flurodeoxyglucose positron emission tomography integrated with computed tomography (18FDG-PET/CT) is a valuable tool for the detection and staging of different types of cancers (especially hematologic cancers and higher stages of breast cancers). However, 18FDG-PET/CT should be avoided during pregnancy because of the high dose of radiation exposure to the fetus (up to 50mGy). [12] Whole-body diffusion-weighted MRI has shown to be feasible in the detection of primary lesions and nodal and distant metastasis in women diagnosed with cancer during pregnancy. Furthermore it can be used as a screening tool for underlying malignancy in case of an aberrant non-invasive prenatal testing. [2,13] Since there are no fetal adverse effects known, this non-ionizing imaging technique can be used safely. If indicated, pineapple juice can be used as an oral negative contrast agent for imaging optimization of the abdomen without harming the fetus.[14]

Single-day protocols for sentinel node procedures are considered safe during pregnancy. [15] Radiopharmaceuticals can be used for these procedures when administered at low doses, not exceeding a fetal exposure of 5mGy. [16] The lowest possible dose of technetium can be locally injected two hours prior to the procedure. In such case, approximately 90% of the technetium will be collected in the sentinel node, resulting in low systemic exposure and minimal fetal risk. Indocyanide green, a near-infrared imaging probe known for its accurate sentinel node detection and very limited placental transfer, is

also widely used in pregnant patients. [17,18] The use of blue dye for the detection of a sentinel node should be avoided since there is a small risk of an anaphylactic reaction (0.1%).[19]

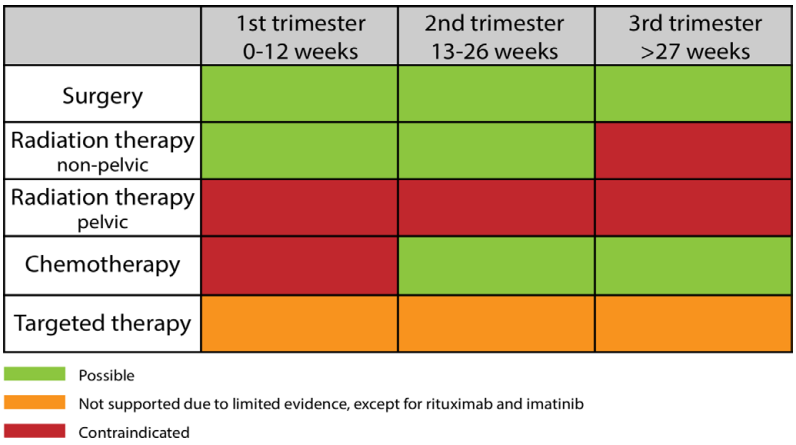


Figure 1. Cancer treatment per trimester.

CANCER TREATMENT IN PREGNANCY

Surgery

Surgery can be performed whenever indicated, irrespective of gestational age (Figure 1). [20] Interventions are preferably performed in the (early) second trimester, minimizing the risk of spontaneous abortion. Morbidity and pregnancy complications, such as preterm delivery and fetal distress, are more common in major abdominal and pelvic procedures due to an enlarging uterus with increased pelvic blood supply.[20] Identical to non-cancer pregnant patients, inferior vena cava compression by the gravid uterus should be reduced by placing the patient in the left-lateral tilt position from 20 weeks of gestation onwards. Tocolytics during surgery should not be given unless contractions are noted. If uterine manipulation is inevitable, post-operative administration of tocolytics can be considered for 48 hours in the late second trimester (when oxytocin receptors are present) and the third trimester of pregnancy.[21]

Laparoscopic interventions result in fewer adverse fetal and maternal events compared with laparotomy and should be chosen over open procedures when oncologically safe and if performed by an experienced surgeon, with limited operation time (90-120 min) and low intra-abdominal pressure (10-13 mmHg).[21,22] An open entry reduces the risk of uterine perforation with a Veress needle. Pelvic lymphadenectomy can be performed until 22 weeks of gestation, both by laparotomy or laparoscopy. [21] Later in pregnancy, the size of the uterus impedes the possibility of a complete pelvic lymph node dissection and should be avoided.

Gestational physiologic changes call for an adapted anesthesiologic approach, with extra safety surveillance to keep blood pressure and maternal oxygenation as stable as possible. If the fetus is viable

(24 weeks of gestation or later, depending on local hospital policies), active management including intraoperative fetal cardiotocography monitoring and lung maturation should be discussed with the parents. Postoperative adequate pain control is important as is intravenous hydration and thromboprophylaxis until the patient is ambulatory.

Systemic Therapy

There are a number of factors that need to be taken into account before systemic therapy during pregnancy is administered, including physiologic changes in pregnancy, gestational age, placental passage, and the pharmacokinetic characteristics of the given drug. Physiologic changes may affect the exposure and efficacy of systemic treatments by influencing their pharmacokinetics with respect to distribution, metabolism and excretion of drugs.

Transplacental transfer of chemotherapeutic drugs occurs by passive diffusion and is therefore based on the drug-specific molecular size, lipid solubility, protein binding and ionization. Since most chemotherapeutic drugs have a low molecular weight and are uncharged and unbound, they can easily cross the human placenta. In baboons, fetal to maternal drug passage ranged from none for docetaxel up to a maximum concentration ratio of 0.58 for carboplatin.[23,24]

Short-term outcomes of children exposed to chemotherapy in utero are generally reassuring; however, long-term outcomes (>6 years) are unknown and the use of many targeted and hormonal therapies should be discouraged until more information on fetal safety is available.

Chemotherapy

Chemotherapy must be avoided in the first trimester of pregnancy to avoid interference with organogenesis (Figure 1). After 12-14 weeks of gestation, administration of most cytotoxic drugs is feasible and considered relatively safe.[25] Standard chemotherapy regimens and doses are preferred using the actual maternal weight during pregnancy. After 35 weeks of gestation chemotherapy is usually discouraged to allow a certain window with regard to the administration scheme for maternal and fetal bone marrow recovery between the last cycle of chemotherapy and delivery. The latter should ideally be planned allowing timely resumption of postpartum chemotherapy if indicated.

Targeted Therapy and Immunotherapy

There are limited preclinical and clinical data on the use of targeted therapy in humans.[26] Targeted therapy is a collective of drugs with different mechanisms of action and characteristics with implications for their use in pregnancy. First, placental passage depends on the class of drugs and their size: large molecules for example, monoclonal antibodies (such as trastuzumab, rituximab) require an active transport via the placenta, which is present starting from the 14th week of gestation. In contrast, small

molecules, such as tyrosine kinase inhibitors can cross the placenta throughout the whole pregnancy. Targeted therapy is aimed at specific tumor-related features, some of which also play integral physiologic roles in fetal development. Consequently, these therapies may lead to an increased risk of fetal morbidity and pregnancy complications, depending on their role in fetal development.

Lambertini et al.[26] have published a comprehensive review on targeted therapy during pregnancy. For the treatment of B cell malignancies, rituximab is essential, and although it seems to be teratogenic during the first trimester,[27] it may be used with caution in the second and third trimester, while paying attention to neonatal lymphocytopenia.[26] Imatinib, a tyrosine kinase inhibitor approved for the management of Philadelphia chromosome positive chronic myeloid leukemia, crosses the placenta and should not be administered during the first trimester. It has been shown to cause malformations when administered during the first trimester in pregnant women, but appears to be safe during the second and third.[26] Angiogenesis inhibitors are teratogenic and have been shown to induce pregnancy loss, skeletal retardations and fetal growth restriction in animal models, due to the crucial role of angiogenesis in the normal development of the placenta and the fetus. Thus, anti-vascular endothelial growth factor and other antiangiogenic drugs are contraindicated during pregnancy. HER-2-targeted therapy trastuzumab, commonly used for treating HER-2 overexpressing breast cancer, is associated with severe oligo-/anhydramnios and subsequent neonatal respiratory failure due to lung hypoplasia when administered in the second or third trimester, probably due to blockage of the epidermal growth factor receptor-2 expressed in the fetal kidney. [28] The use of trastuzumab is often delayed until after delivery. Regarding immunotherapy, PD1/PD-L1 and CTLA-4 interactions appear to play key roles in maintaining normal fetal tolerance; not surprisingly immune checkpoint inhibitors such as anti-PD1/PD-L1 agents have been shown to increase the rate of spontaneous abortions in animals. [29] However, there are a few case reports of pregnant melanoma patients being treated during the first trimester without miscarriage. [30,31] Based on the limited evidence available, the use of targeted therapies commonly administered for the treatment of cancer is not supported during pregnancy and should ideally be postponed until after delivery, except for rituximab and imatinib which may be given in the second and third trimester (Figure 1). Nevertheless, accidental short-term exposure to biologic agents during the first trimester does not justify termination of pregnancy per se.

Supportive Treatment

Supportive medication as part of systemic treatment is considered safe for a number of drugs. Antiemetics may be administered during pregnancy, including metoclopramide and serotonin receptor antagonists, [32] but safety has not been determined for neurokinin 1 inhibitors. [33] Use of betamethasone or dexamethasone as premedication is discouraged due to almost 100% placental passage to the fetus,

and these are better replaced by steroids that are metabolized in the placenta including methyl-prednisolone or hydrocortisone. There is ongoing debate about the use of growth factors, such as granulocyte colony stimulating factor and erythropoietin, although the former has been shown to be safe during pregnancy, permitting dose dense schedules. [34]

Radiation Therapy

On account of high fetal radiation dosages and severe or lethal consequences to the fetus, pelvic irradiation should never be performed intentionally during pregnancy (Figure 1). [9] Generally, radiotherapy for non-pelvic cancers is limited to the first trimester, when the uterus is still at a distance from the irradiation field. The total dose of fetal irradiation comprises a combination of internal scatter, leakage radiation and external scatter. The internal scatter depends on the source of irradiation and the proximity to the fetus. [9]

Since the impact of irradiation on the fetus depends on gestational age and radiation dose, careful planning in agreement with the patient is essential. [9] Maternal and fetal consequences of treatment options with and without radiation should be carefully discussed with both patient and partner. Using a phantom model, it is recommended that a physicist calculates the fetal radiation dose and modifications to the treatment plan such as changing the field size, angle, and radiation energy should be considered where possible.

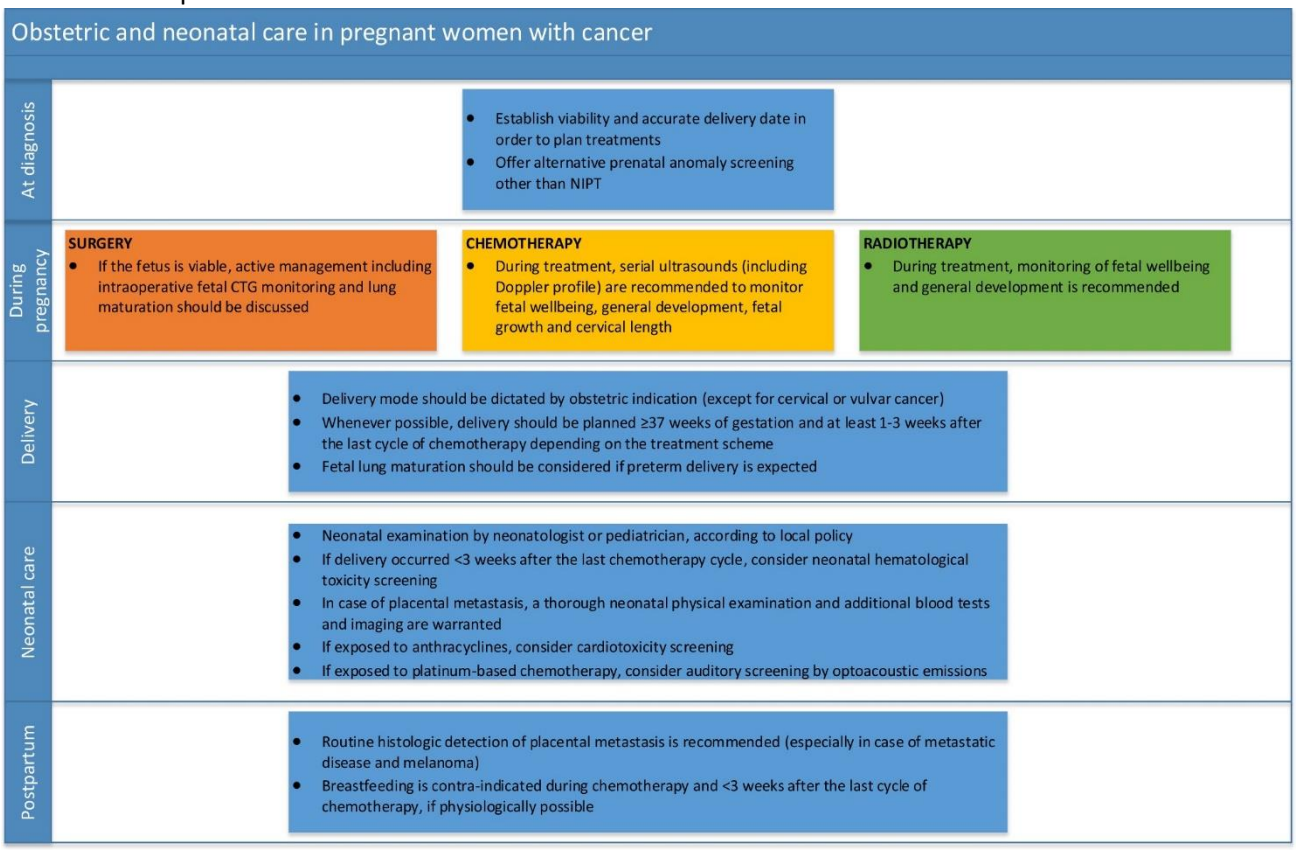


Figure 2. Obstetric and neonatal care in pregnant women with cancer. CTG, cardiotocography; NIPT, non-invasive prenatal testing.

OBSTETRIC AND PERINATAL MANAGEMENT

Planning obstetric and perinatal management in women with cancer involves close collaboration between oncologic and obstetric disciplines because of all the different aspects that need to be taken into account (Figure 2). Pregnancy dating should be done early in gestation to permit accurate estimation of gestational age at diagnosis and treatment.

Obstetric Management

Non-invasive prenatal testing

Non-invasive prenatal testing is a widely used method to screen for common fetal aneuploidies, primarily designed for trisomy 21 (Down syndrome), trisomy 18 (Edwards syndrome) and trisomy 13 (Patau syndrome). Non-invasive prenatal testing analyzes circulating cell-free DNA (cfDNA) fragments in the blood of pregnant women. A small proportion of these fragments (10%-15% between 10 and 20 weeks of gestation) originates from placental cells, and hence represents fetal DNA. But as the majority of cfDNA is from maternal origin it may also detect maternal chromosomal abnormalities (Figure 3). [35] Occult maternal malignancies have been identified as an incidental finding following a deviating non-invasive prenatal testing result, not being consistent with the fetal genetic constitution. [36] As the use of non-invasive prenatal testing is increasingly being expanded to low-risk pregnancies - in some countries it is even offered as a first-tier test to all pregnant women - and its scope is being broadened beyond aneuploidy screening, more discordant results are expected to be identified. When a non-invasive prenatal testing result is suggestive of a maternal cancer, the result should be confirmed by a second non-invasive prenatal testing and comparison of the result with the chromosomal profile in maternal tissue. [2] A multidisciplinary team of specialists is advised to be involved in the diagnostic workup and adequate counselling of the pregnant woman throughout the process. [37] As a consequence, non-invasive prenatal testing in women with a known cancer diagnosis is non-informative and alternative prenatal screening testing should be offered. [38]

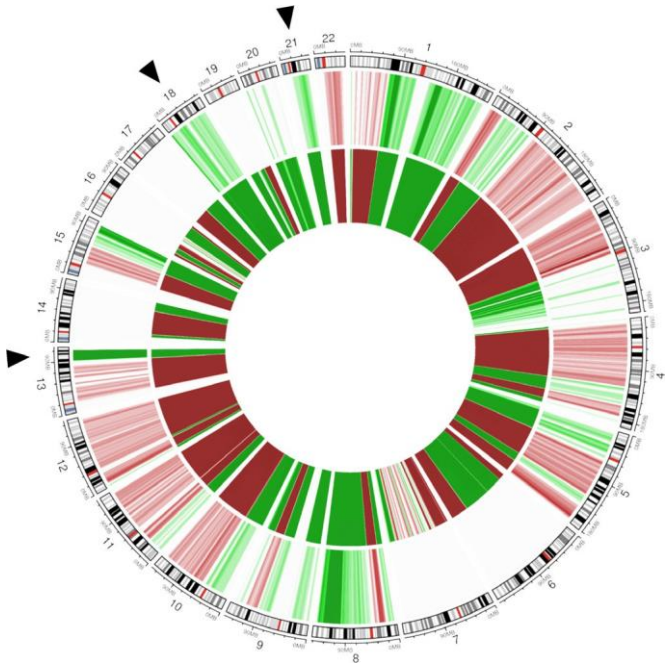


Figure 3 Non-invasive prenatal testing. Circos plot showing chromosomal anomalies detectable in plasma cell-free DNA (cfDNA) and matched tumor biopsy DNA of a pregnant woman who was 8 weeks' pregnant with a known breast cancer diagnosis. The genomic representation profile of the autosomal chromosomes is shown in clockwise order, aligned with chromosomal ideograms (outer circle).Chromosomal anomalies representing gain are indicated in green; those representing losses are shown in red. Color grades are used to indicate the amplitude of the copy number alterations (CNAs). The middle circle depicts the genome-wide, non-invasive prenatal testing (NIPT) profile in plasma cfDNA with elevated anomalies observed for chromosomes 21, 18, and 13 (indicated by black arrows). On a genome-wide view, (sub)chromosomal imbalances across multiple autosomal chromosomes can be observed. The inner circle shows the copy number profile of matched tumor DNA extracted from formalin-fixed paraffin-embedded tumor biopsy material (whole-genome low-pass sequencing, 0.1 x coverage). Comparison of both profiles reveals that the (sub)chromosomal CNAs and aneuploidies observed in plasma cfDNA are derived from tumor DNA. Adapted with permission from Lenaerts (2019).[38]

Obstetric Ultrasound

Available large case series reveal that neonates prenatally exposed to chemotherapy are at risk of being born small for gestational age, defined as a customized birth weight percentile below 10.[5] Besides constitutionally small neonates, explained by inherited factors, this definition also incorporates fetuses that did not reach their growth potential and are pathologically growth restricted. In the pregnant cancer population, risk factors for impaired fetal growth such as maternal age, cancer (especially hematologic cancers), poor general health, malnutrition and treatment-related stress are common. Whether the chosen regimen of cytotoxic drugs during pregnancy affects the neonatal growth potential is uncertain. Growth restricted neonates are at risk for adverse outcomes in the short- and long-term.[39] In order to detect fetal growth restriction, 2-weekly prenatal ultrasound to monitor fetal growth and amount of amniotic fluid during the course of antenatal chemotherapy is recommended.[21] This prenatal information will inform obstetricians on fetal wellbeing and enable them to intervene at signs of fetal compromise. A cardiotocogram can provide additional information. Because chemo-

therapy, especially platinum and non-platinum alkylating agents, is associated with preterm contractions and delivery, [5] expert advice includes regular cervical length monitoring (2-4 weekly) in every pregnant patient receiving antenatal chemotherapy. [21] Theoretically, preterm labor might be explained by stress-related activation of the maternal hypothalamic-pituitary-adrenal axis or chemotherapy-induced apoptosis in fetal membranes causing preterm membrane rupturing. Physicians should be aware of preterm contractions following chemotherapy with a low threshold for admission for observation and administration of intravenous fluids and tocolytics.

Perinatal Management

Delivery

Delivery in oncologic patients is usually planned in order to minimize the treatment-free interval and not impair maternal outcome. Whenever possible, delivery should be planned after 37 weeks of gestation in order to avoid prematurity-related neonatal complications and long-term impairment. [4] Cesarean section rate in pregnant cancer patients is observed to be over 30%, which is higher compared with the reported worldwide rate of 21%.[40] This higher rate is partly explained by the high proportion of preterm deliveries and the desire of a planned and controlled delivery in oncologic patients that are subject to psychologic stress and physical exhaustion. Unless obstetrically contraindicated, a vaginal delivery is desired with fewer neonatal and maternal complications. Vaginal delivery is contraindicated for most cervical and vulvar cancers because of the potential for implantation of cancer cells in the vaginal tear/episiotomy site. [21]

Delivery within three weeks of chemotherapy regimens, or shorter intervals in cases of 2-weekly or weekly schemes, should be avoided. This safety window allows time for the placenta to metabolize the chemotherapy (especially important for the preterm infant), and for resolution of any myelosuppression on the part of mother and fetus. A report on 49 neonates prenatally exposed to chemotherapy within four weeks of birth reported a 33% incidence of transient neutropenia; [41] La Nasa et al. reported an incidence of 20% of neutropenia at birth in neonates delivered 22-28 days after chemotherapy. [42] In contrast, 3 out of 54 neonates (5.5%) prenatally exposed to chemotherapy more than four weeks before delivery were born with neutropenia. A neonatal blood test after birth should identify risks for nosocomial infections.

Placental Examination

Reliable incidence rates of metastatic involvement of the placenta in women with cancer are lacking, as routine histologic detection of placental metastasis is not always performed. Based on approximately 100 published cases, placental metastasis is rare, but may occur in women with malignant melanoma and metastatic disease of any cancer type. [43] Although even rarer, it is often the only indication

for early detection of neonatal metastasis (17% in the group of placental involvement). [44] Neonatal/fetal metastases have been found mainly in patients with melanoma, and incidentally in lung cancer and leukemia. Placental metastases are mainly located in the intervillous space and to a lesser extent in the villi, probably due to the placental barrier protecting the fetus from hazardous substances in the maternal circulation. Although based on limited evidence, only villous involvement has been described in association with neonatal metastasis. To this end, histologic examination of the placenta is crucial and recommended for the detection of microscopic placental metastasis and the identification of potential fetal involvement, especially in women with melanoma or with advanced disease.

As mentioned earlier, fetal growth restriction is a well-known obstetric complication in pregnancies complicated by cancer. [5] Uteroplacental vascular insufficiency and the subsequent impact on placental development accounts for the majority of fetal growth restriction in the non-cancer population. [45] A direct damaging effect of chemotherapy to the placenta has not been identified yet, but is strongly suspected, as placental weight is significantly lower after maternal chemotherapy treatment. [46] Placental examination in women with cancer, especially those with fetal growth restriction, will provide more insight into cancer treatment-induced placental effects and may influence treatment choice and obstetric management in the future.

Lactation

Because of both short- and long-term health benefits, the World Health Organization (WHO) recommends that infants are exclusively breastfed to 6 months of age, with breastfeeding continuing to be an important part of the diet up to two years. [47] For pregnant cancer patients breastfeeding is often highly desired for emotional bonding and as a healthy compensation after prenatal exposure to cancer treatment. However, in clinical practice nursing is discouraged when cytotoxic treatment continues after delivery. Chemotherapy is able to pass into human milk, and although the oral bioavailability is low, case reports have described neutropenia in infants that were breastfed during cancer treatment. [48] A safety period of three weeks between the last administration of most non-platinum chemotherapeutic agents and nursing is strongly recommended. For platinum derivates, the long half-life is a concern, and a case has been described with detectable platinum levels in breast milk more than three weeks after last exposure. [49] Moreover, both chemotherapy and cancer itself might negatively affect the bacterial and metabolic compositions of human milk. [50] Cancer patients that received chemotherapy report reduced milk production and more difficulties to breastfeed compared to untreated patients, possibly explained by lobular atrophy with fibrosis of breast tissue following chemotherapy exposure. [51] For breast cancer patients reduced milk production should be expected from the affected breast after breast conservation therapy. Breast feeding is not recommended in women with hormone receptor-positive breast cancer due to the necessity of adjuvant endocrine therapy. [52] Cancer patients

that consider breastfeeding should be counseled about the risks of low milk production, breast infections and the hampering of diagnostic and therapeutic procedures in case of breast cancer because of breast engorgement.

Neonatal and Pediatric Management

Children of mothers with cancer during pregnancy require an individualized approach to postnatal care. The different aspects of neonatal and pediatric care depend on the type of cancer, type of treatment exposure in utero and the timing thereof. Whether every neonate, independent of treatment exposure, should be examined by a neonatologist or pediatrician is based on local protocols. A neonatal complete blood count test is strongly advised to identify myelosuppression, especially if the last chemotherapy cycle was given less than three weeks before delivery. In cases with placental metastasis or a suspicion of neonatal metastasis, a thorough physical examination, additional liver panel, abdominal ultrasound and thorough skin examination, in case of melanoma, should be performed to detect any neonatal disease. Because of anthracycline-related cardiotoxicity in childhood cancer survivors, [53] a cardiotoxicity screening including echocardiography is recommended for children exposed to anthracyclines in utero. Children exposed to platinum-based chemotherapeutics should be screened for auditory dysfunction using otoacoustic emissions until the age of 5 years, followed by audiometry at later ages. [21] Additionally, on indication, a consultation with a physiotherapist for developmental follow-up and a geneticist for screening of genetic predisposition to cancer could be offered. The frequency of further visits depends on the existence of fetal metastasis or abnormalities found during the initial visits and examinations.

OBSTETRIC, FETAL AND PEDIATRIC OUTCOME AFTER ONCOLOGIC TREATMENT

Obstetric and Fetal Outcome

No studies have shown an improved maternal survival with termination of pregnancy; control groups are often lacking and stage of disease is not consistently reported limiting the ability to compare severity of disease between women continuing versus terminating a pregnancy. Termination can be considered in cases of aggressive or advanced cancer in early pregnancy.

It is well established that cytotoxic drugs should be initiated after the vulnerable period of organogenesis and exposure to chemotherapy during the first trimester of pregnancy is associated with a congenital malformation rate of 10-20%. Overall, reported rates of minor and major birth defects in population-based studies as well as cohort studies in the pregnant cancer population are similar to what is expected in the general population. [5]

Chemotherapy crosses the placenta and can impact fetal growth, as suggested by several large cohort studies that report a high incidence of small for gestational age or fetal growth restriction, up to 21%, in the pregnant cancer population. [5] The background incidence of fetal growth restriction varies according to the population, geographic location, and standard growth curves used as reference. In general, 4 to 8% of all infants born in developed countries are classified as growth-restricted. [54] Of note, the underlying maternal disease, cytotoxic treatment during pregnancy, cachexia, cancer-related psychologic stress and malnutrition are important cofactors in the incidence of fetal growth restriction in pregnancies complicated by maternal cancer (Figure 4). The highest rates of small for gestational age are reported in hematologic and gastro-intestinal cancers. [5] For chemotherapy, de Haan et al. reported the highest odds ratio for fetal growth restriction with platinum agents (OR 3.12, 95% CI 1.45-6.70) and taxanes (OR 2.07, 95% CI 1.11-3.86).

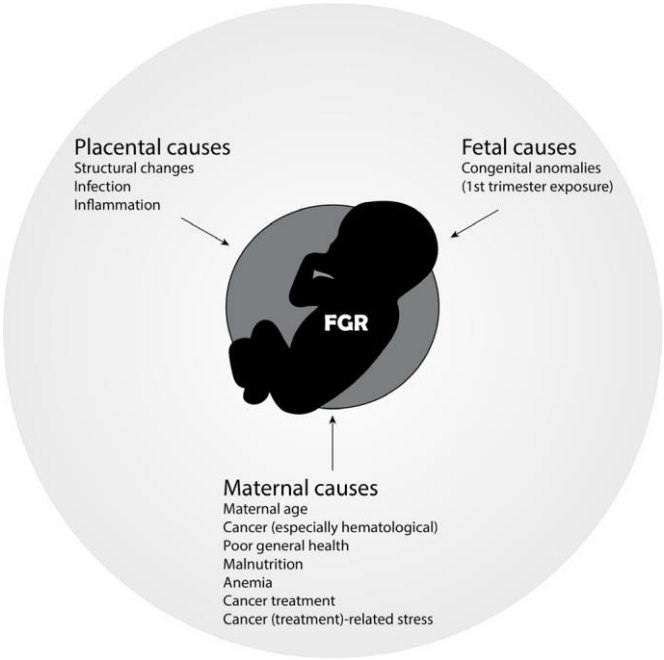


Figure 4 Etiologies of fetal growth restriction (FGR) in women with cancer.

Preterm birth is common, both iatrogenic because of oncologic treatment planning and spontaneous following chemotherapy-provoked preterm contractions. Due to the long-term morbidities for preterm children, avoiding iatrogenic elective preterm births is recommended, whenever possible. [55]
Bone marrow toxicity can occur in neonates prenatally exposed to chemotherapy and fetal anemia, secondary to cancer or treatment can also be detected during pregnancy by Doppler studies. [56] The combination of poor maternal general health, pancytopenia, systemic illness, oncology-related stress and cytotoxic drugs might endanger the fetus and the placental function leading to increased risk of intrauterine fetal death, especially in patients with acute leukemia in which intrauterine fetal death is more common compared to other cancers.

Large cohort studies comparing patients that received chemotherapy during pregnancy and patients with a deferral of treatment until after delivery revealed an overall obstetric complication rate of 13%-21%.[57,58] Premature preterm rupture of membranes and preterm delivery occurred more frequently in the exposed group. Several large population-based studies comparing obstetric outcomes between patients with pregnancy-associated cancer and patients without a cancer diagnosis have been published.[59] Maternal infections, hypertension, venous-thrombotic events and postpartum blood transfusions appear to be more common in the pregnant cancer population.[40] On account of the hypercoagulable state of pregnancy, low molecular weight heparins during pregnancy and more importantly until six weeks after delivery should be considered.

Pediatric Outcome

Amant et al. reported on 129 children (median age, 22 months) exposed to chemotherapy in utero, that showed no significant difference in cognitive outcome and development compared to healthy controls, matched by gestational age at delivery and test age.[4] No significant differences were noted in cognitive skills, academic achievement or behavioral competence between 35 chemotherapy exposed children (mean age at evaluation, 4.5±3.1 years) and 22 children (4.9±2.6 years) of women with cancer who did not receive chemotherapy prior to delivery.[60] A normal educational performance was also reported by Aviles et al. reporting 84 children exposed to chemotherapy in utero for maternal hematologic cancer (mean follow-up 18.7 [range 6-29] years).[61] All children had adequate neurologic and psychologic evaluations. These studies found no adverse effects of chemotherapy on postnatal cognitive function.[4,61] A recent study of 132 children born to women with cancer, of whom 97 were exposed to chemotherapy, showed normal development at the age of 6 years.[7] Subtle differences between these children and matched healthy controls were found in verbal intelligence in favour of the latter. Interestingly, in a post-hoc analysis, the difference in verbal intelligence was more distinct in the group of children who lost their mother to cancer. Hence, detection of verbal development delays and early psychosocial stimulation to prevent underdevelopment could be considered. In a group of 21 newborns exposed to anthracycline/cyclophosphamide-based chemotherapy in utero, no differences in fetal brain growth were found compared with a group of healthy controls.[62]

The child of a pregnant cancer patient is usually exposed to multiple anticancer drugs, complicating the interpretation of the possible effects of a single drug on their long-term outcome. As previously mentioned, the administration of anthracyclines during childhood is known to cause short- and long-term cardiotoxic effects.[53] Available cohort studies of children prenatally exposed to chemotherapy are relatively small and represent a maximum follow-up of 20 years. Electrocardiographic results are reassuring.[55]

In childhood cancer survivors, overall hearing loss is seen in up to 48% of children exposed to platinum-based agents with age being the most important negatively associated risk factor. [63] In particular, cisplatin is highly associated with ototoxicity. Hearing loss following cisplatin exposure in utero is also reported, [55,64] but factors such as a middle ear infection, the use of aminoglycosides and neurodevelopmental problems potentially confound this result.

To date, available long-term outcome studies of children exposed to chemotherapy in utero suggest that chemotherapy is not related to insufficient postnatal growth or impaired cognitive or cardiac function. However data on long-term outcome are scarce and more studies are needed to provide further insight into long-term safety, including the cancer risk and fertility of the offspring. The International Network on Cancer, Infertility and Pregnancy (INCIP) will continue their work by evaluating the development of children of women with cancer during pregnancy until the age of 18 years and beyond.

CONCLUSIONS

In recent decades, research on the feasibility and safety of oncologic treatment during pregnancy has expanded resulting in more ongoing pregnancies while treating maternal cancer without delay. As pregnant women with cancer, especially those treated with chemotherapy, face certain obstetric risks, pregnancy monitoring is crucial as is the involvement of perinatologists and neonatologists within a multidisciplinary setting. Moreover, patients and their partners should be supported and encouraged to be actively involved in decision-making regarding oncologic treatment and consequential perinatal decisions. In addition, professional guidance after delivery concerning breastfeeding, physiologic and psychologic wellbeing is often highly desired.

REFERENCES

1 Stensheim, H., Møller, B., van Dijk, T. & Fosså, S. D. Cause-specific survival for women diagnosed with cancer during pregnancy or lactation: a registry-based cohort study. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology* **27**, 45-51 (2009).

2 Lenaerts, L., Jatsenko, T., Amant, F. & Robert Vermeesch, J. Noninvasive Prenatal Testing and Detection of Occult Maternal Malignancies. *Clinical chemistry* **65**, 1484-1486 (2019).

3 Eibye, S., Kjær, S. K. & Mellemkjær, L. Incidence of pregnancy-associated cancer in Denmark, 1977-2006. *Obstet Gynecol* **122**, 608-617 (2013).

4 Amant, F. *et al.* Pediatric Outcome after Maternal Cancer Diagnosed during Pregnancy. *N Engl J Med* **373**, 1824-1834 (2015).

5 de Haan, J. *et al.* Oncological management and obstetric and neonatal outcomes for women diagnosed with cancer during pregnancy: a 20-year international cohort study of 1170 patients. *Lancet Oncol* (2018).

6 Masturzo, B. *et al.* Impact of cancer in the management of delivery: 10 years of variations. *J Matern Fetal Neonatal Med* **33**, 2006-2011 (2020).

7 Vandenbroucke, T. *et al.* Child development at 6 years after maternal cancer diagnosis and treatment during pregnancy. *European Journal of Cancer.* 138:57-67 (2020).

8 Valentin, J. Biological Effects after Prenatal Irradiation (Embryo and Fetus). *Annals of the ICRP* **33**, 1-206 (2003).
9 Kal, H. B. & Struikmans, H. Radiotherapy during pregnancy: fact and fiction. *The Lancet. Oncology* **6**, 328-333 (2005).
10 Wakeford, R. & Little, M. P. Risk coefficients for childhood cancer after intrauterine irradiation: a review. *International journal of radiation biology* **79**, 293-309 (2003).
11 American College of Radiology. *ACR manual on contrast media. Version 2020* (2020).
12 American College of Radiology. *ACR-SPR Practice parameter for imaging pregnant or potentially pregnant adolescents and women with ionizing radiation. Resolution 39* (2018).
13 Han, S. N. *et al.* Feasibility of whole-body diffusion-weighted MRI for detection of primary tumour, nodal and distant metastases in women with cancer during pregnancy: a pilot study. *European Radiology* **28**, 1862-1874 (2017).
14 Frisch, A., Walter, T. C., Hamm, B. & Denecke, T. Efficacy of oral contrast agents for upper gastrointestinal signal suppression in MRCP: A systematic review of the literature. *Acta Radiol Open* **6**, 2058460117727315 (2017).
15 Han, S. N. *et al.* Axillary staging for breast cancer during pregnancy: feasibility and safety of sentinel lymph node biopsy. *Breast cancer research and treatment* **168**, 551-557 (2018).
16 Adelstein, S. J. Administered Radionuclides in Pregnancy. *Surgical Endoscopy*, 1-32 (1999).
17 Rychlik, A., Marin, S., De Santiago, J. & Zapardiel, I. Utility of Laparoscopic Indocyanine Green-Guided Sentinel Node Biopsy in Open Cervical Cancer Surgery. *International journal of gynecological cancer : official journal of the International Gynecological Cancer Society* **26**, 1288-1289 (2016).
18 Rubinchik-Stern, M., Shmuel, M., Bar, J., Eyal, S. & Kovo, M. Maternal-fetal transfer of indocyanine green across the perfused human placenta. *Reprod Toxicol* **62**, 100-105 (2016).
19 Bézu, C. *et al.* Anaphylactic response to blue dye during sentinel lymph node biopsy. *Surgical Oncology* **20**, e55-e59 (2011).
20 Peccatori, F. A. *et al.* Cancer, pregnancy and fertility: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* **24 Suppl 6**, vi160-170 (2013).
21 Amant, F. *et al.* Gynecologic cancers in pregnancy: guidelines based on a third international consensus meeting. *Ann Oncol* **30**, 1601-1612 (2019).
22 Obermair, A. *et al.* Incidence of adverse events in minimally invasive vs open radical hysterectomy in early cervical cancer: results of a randomized controlled trial. *Am J Obstet Gynecol* **222**, 249.e241-249.e210 (2020).
23 Van Calsteren, K. *et al.* Transplacental transfer of anthracyclines, vinblastine, and 4-hydroxy-cyclophosphamide in a baboon model. *Gynecol Oncol* **119**, 594-600 (2010).
24 Calsteren, K. V. *et al.* Transplacental transfer of paclitaxel, docetaxel, carboplatin, and trastuzumab in a baboon model. *International journal of gynecological cancer : official journal of the International Gynecological Cancer Society* **20**, 1456-1464 (2010).
25 Cardonick, E. & Iacobucci, A. Use of chemotherapy during human pregnancy. *The Lancet. Oncology* **5**, 283-291 (2004).
26 Lambertini, M., Peccatori, F. A. & Azim, H. A., Jr. Targeted agents for cancer treatment during pregnancy. *Cancer treatment reviews* **41**, 301-309 (2015).
27 Lishner, M. *et al.* Hematologic Malignancies in Pregnancy: Management Guidelines From an International Consensus Meeting. *J Clin Oncol* **34**, 501-508 (2016).
28 Azim, H. A., Jr. *et al.* Pregnancy occurring during or following adjuvant trastuzumab in patients enrolled in the HERA trial (BIG 01-01). *Breast Cancer Res Treat* **133**, 387-391 (2012).
29 Poulet, F. M., Wolf, J. J., Herzyk, D. J. & DeGeorge, J. J. An Evaluation of the Impact of PD-1 Pathway Blockade on Reproductive Safety of Therapeutic PD-1 Inhibitors. *Birth defects research. Part B, Developmental and reproductive toxicology* **107**, 108-119 (2016).
30 Burotto, M. *et al.* Viable Pregnancy in a patient with metastatic melanoma treated with double checkpoint immunotherapy. *Seminars in oncology* **45**, 164-169 (2018).
31 Mehta, A., Kim, K. B. & Minor, D. R. Case Report of a Pregnancy During Ipilimumab Therapy. *Journal of global oncology* **4**, 1-3 (2018).
32 Pasternak, B., Svanström, H. & Hviid, A. Ondansetron in pregnancy and risk of adverse fetal outcomes. *N Engl J Med* **368**, 814-823 (2013).
33 Briggs, G., Freeman, R. & Yaffe, S. *Drugs in pregnancy and lactation : a reference guide to fetal and neonatal risk*. (Wolters Kluwer Health/Lippincott Williams & Wilkins, 2011).

34 Cardonick, E., Irfan, F. & Torres, N. The Use of Neupogen (Filgrastim) or Neulasta (Pegfilgrastim) during Pregnancy When Chemotherapy Is Indicated for Maternal Cancer Treatment *Journal of Cancer Therapy* **3**, 157-161 (2012).

35 Brison, N. *et al.* Accuracy and clinical value of maternal incidental findings during noninvasive prenatal testing for fetal aneuploidies. *Genetics in medicine : official journal of the American College of Medical Genetics* **19**, 306-313 (2017).

36 Amant, F. *et al.* Presymptomatic Identification of Cancers in Pregnant Women During Noninvasive Prenatal Testing. *JAMA Oncol* **1**, 814-819 (2015).

37 Saes, L. *et al.* [Incidental detection of maternal malignancy in non-invasive prenatal test]. *Ned Tijdschr Geneeskd* **163** (2019).

38 Lenaerts, L., Van Calsteren, K., Che, H., Vermeesch, J. R. & Amant, F. Pregnant women with confirmed neoplasms should not have noninvasive prenatal testing. *Prenatal diagnosis* **39**, 1162-1165 (2019).

39 Lees, C. *et al.* Perinatal morbidity and mortality in early-onset fetal growth restriction: cohort outcomes of the trial of randomized umbilical and fetal flow in Europe (TRUFFLE). *Ultrasound Obstet Gynecol* **42**, 400-408 (2013).

40 Lee, Y. Y. *et al.* Incidence and outcomes of pregnancy-associated cancer in Australia, 1994-2008: a population-based linkage study. *Bjog* **119**, 1572-1582 (2012).

41 Reynoso, E. E. *et al.* Acute leukemia during pregnancy: the Toronto Leukemia Study Group experience with long-term follow-up of children exposed in utero to chemotherapeutic agents. *J Clin Oncol* **5**, 1098-1106 (1987).

42 La Nasa, M., Gaughan, J. & Cardonick, E. Incidence of Neonatal Neutropenia and Leukopenia After In Utero Exposure to Chemotherapy for Maternal Cancer. *Am J Clin Oncol* **42**, 351-354 (2019).

43 Pavlidis, N. & Pentheroudakis, G. Metastatic involvement of placenta and foetus in pregnant women with cancer. *Recent Results Cancer Res* **178**, 183-194 (2008).

44 Alexander, A. *et al.* Metastatic melanoma in pregnancy: risk of transplacental metastases in the infant. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology* **21**, 2179-2186 (2003).

45 Burton, G. J. & Jauniaux, E. Pathophysiology of placental-derived fetal growth restriction. *Am J Obstet Gynecol* **218**, S745-s761 (2018).

46 Verheecke, M. *et al.* Genetic and microscopic assessment of the human chemotherapy-exposed placenta reveals possible pathways contributive to fetal growth restriction. *Placenta* **64**, 61-70 (2018).

47 World Health Organization. Vol. 12-13 (Sixty-fifth World Health Assembly, Geneva, 21–26 May 2012. Resolutions and decisions, annexes. Geneva, 2012).

48 Durodola, J. I. Administration of cyclophosphamide during late pregnancy and early lactation: a case report. *J Natl Med Assoc* **71**, 165-166 (1979).

49 Griffin, S. J. *et al.* Transfer of carboplatin and paclitaxel into breast milk. *J Hum Lact* **28**, 457-459 (2012).

50 Ma, Z. S., Li, L., Li, W., Li, J. & Chen, H. Integrated network-diversity analyses suggest suppressive effect of Hodgkin's lymphoma and slightly relieving effect of chemotherapy on human milk microbiome. *Sci Rep* **6**, 28048 (2016).

51 Stopenski, S., Aslam, A., Zhang, X. & Cardonick, E. After Chemotherapy Treatment for Maternal Cancer During Pregnancy, Is Breastfeeding Possible? *Breastfeed Med* **12**, 91-97 (2017).

52 Johnson, H. M. & Mitchell, K. B. ABM Clinical Protocol #34: Breast Cancer and Breastfeeding. *Breastfeed Med* **15**, 429-434 (2020).

53 Lipshultz S., E. *et al.* Late Cardiac Effects of Doxorubicin Therapy for Acute Lymphoblastic Leukemia in Childhood. *The New England journal of medicine* **324**, 808-815 (1991).

54 Resnik, R. & Creasy, R. K. in *Creasy and Resnik's Maternal-Fetal Medicine: Principles and Practice* 635-650 (Elsevier, 2009).

55 Amant, F. *et al.* Long-term cognitive and cardiac outcomes after prenatal exposure to chemotherapy in children aged 18 months or older: an observational study. *Lancet Oncol* **13**, 256-264 (2012).

56 Mari, G. *et al.* Diagnosis of fetal anemia with Doppler ultrasound in the pregnancy complicated by maternal blood group immunization. *Ultrasound Obstet Gynecol* **5**, 400-405 (1995).

57 Loibl, S. *et al.* Treatment of breast cancer during pregnancy: an observational study. *Lancet Oncol* **13**, 887-896 (2012).

58 Maggen, C. *et al.* Obstetric and maternal outcomes in patients diagnosed with Hodgkin lymphoma during pregnancy: a multicentre, retrospective, cohort study. *The Lancet. Haematology* **6**, e551-e561 (2019).

59 Maggen, C., van Gerwen, M., Van Calsteren, K., Vandenbroucke, T. & Amant, F. Management of cancer during pregnancy and current evidence of obstetric, neonatal and pediatric outcome: a review article. *International journal of gynecological cancer : official journal of the International Gynecological Cancer Society* (2019).

60 Cardonick, E. H., Gringlas, M. B., Hunter, K. & Greenspan, J. Development of children born to mothers with cancer during pregnancy: comparing in utero chemotherapy-exposed children with nonexposed controls. *American Journal of Obstetrics and Gynecology* **212**, 658.e651-658 (2015).

61 Avilès, A. & Neri, N. Hematological malignancies and pregnancy: A final report of 84 children who received chemotherapy in utero. *Clinical Lymphoma* **2**, 173-177 (2001).

62 Passera, S. *et al.* Effects of in-utero exposure to chemotherapy on fetal brain growth. *International journal of gynecological cancer : official journal of the International Gynecological Cancer Society* **29**, 1195-1202 (2019).

63 Yancey, A. *et al.* Risk factors for cisplatin-associated ototoxicity in pediatric oncology patients. *Pediatric Blood Cancer* **59**, 144-148 (2012).

64 Geijteman, E. C., Wensveen, C. W., Duvekot, J. J. & van Zuylen, L. A child with severe hearing loss associated with maternal cisplatin treatment during pregnancy. *Obstetrics and gynecology* **124**, 454-456 (2014).

Chapter 3 Objectives and outline of this thesis

Although multidisciplinary care has been widely adopted as the optimal approach for providing care in the oncological field, there is little qualitative or quantitative data available to determine the impact of an MDAB on physician's satisfaction and patient outcomes. The first objective of this thesis was to evaluate the impact of an MDAB in the context of cancer in pregnancy. The second objective was to tackle knowledge gaps encountered by the MDAB using data from the INCIP and the cases identified by the MDAB.

Part I of this thesis consisted of this general introduction of the topic. Next to that, an introductory state of the art review on diagnosis and treatment of pregnant women with cancer at the beginning of this PhD trajectory in 2020 was presented.

In **Part II** of this thesis ('Pooling knowledge: an Advisory Board on Cancer, Infertility and Pregnancy'), we describe how the knowledge of experts in the field of cancer in pregnancy can be pooled in MDABs in order to improve the care of this group of patients in Europe and worldwide. In **Chapter 4,** we provide an insight into the current international organisation of care for pregnant patients with cancer and we have identified the current gaps in knowledge by analysing the results of a survey study. In **Chapter 5**, we show the experiences from the first ten years of the Dutch MDAB on cancer and pregnancy. **Chapter 6** describes the formation of an active multidisciplinary network of (inter)national experts with knowledge of cancer and pregnancy or fertility preservation in the ABCIP. It describes the establishment of a web-based platform, www.ab-cip.org, which allows caregivers to request advice from the ABCIP on the treatment of their pregnant patients with cancer or patients with a desire to preserve their fertility before the start of oncological treatment.

By receiving requests for advice through ABCIP, gaps in knowledge were identified. In **Part III** ('Clinical challenges in the field of Cancer in Pregnancy'), we aimed to contribute to the current knowledge of some of these rare situations and novel treatment options using the INCIP database. We investigated three specific patient populations. First, **Chapter 7** presents a cohort study of all maternal deaths related to cancer in pregnancy in the INCIP registry. Maternal death had only been described as part of a larger cohort and thus there was a lack of information about the group of women with a poor prognosis and the precautions that needed to be taken for the mother and her family.
Secondly, we received questions about women with sarcoma in pregnancy and observed only case reports and small case series in the literature. Therefore, in **Chapter 8**, we describe all cases of sarcoma in pregnancy from INCIP and performed a review of literature.
Thirdly, since knowledge about hematologic malignancies in pregnancy was based on outdated guidelines and small cohort studies, we assembled a group of experts in the field to formulate a guideline paper regarding the most recent data on haematological malignancies during pregnancy. This guideline is described in **Chapter 9**.
New treatment strategies pose a challenge in pregnancy. Currently, immunotherapy is emerging as potential treatment in many types of cancer and is shifting from last resort or salvage treatment to first-line or neo-adjuvant treatment to improve survival. Therefore, we wanted to provide an up-to-date overview on novel treatment modalities in pregnancy. We have summarised all the preclinical and clinical information on immunotherapy during pregnancy in a review paper in **Chapter 10.**

Furthermore, we have also described two 'first in literature' cases. The first is a case report of a severe immune-related adverse event in the child after in utero exposure to pembrolizumab in **Chapter 11** and the second is the use of proton therapy for a nasopharyngeal carcinoma during pregnancy in **Chapter 12.** Cases like this are of extremely important for increasing the knowledge of potential treatments and dangers of treatment in patients with cancer in pregnancy. Tihs will help to improve the daily practice of the ABCIP.

Part IV presents the general discussion and recommendations for further research.

Part II Pooling knowledge: an Advisory Board for Cancer, Infertility and Pregnancy

Chapter 4 Results of an international survey on the current organization of care for pregnant women with cancer

Joosje Heimovaara, Kristel Van Calsteren, Christianne Lok, Andrew Evens, Jorge Hoegl, Andres Ferber, Andreina Fernandes, Ingeborg Vriens, Lia van Zuylen, Frédéric Amant

Acta Obstetricia et Gynaecologica Scandinavica, April 2024.

ABSTRACT

The global incidence of cancer is increasing, including its incidence in women of reproductive age. Still, physicians encounter this situation rarely, which could lead to substandard care. This research sought to explore opportunities to improve future care for pregnant women with cancer, by describing the outcomes of a survey distributed to physicians all over the world focusing on clinical experience with pregnant women with cancer, the organization of care and current gaps in knowledge. We included 249 responses from physicians working across 36 countries. Responses demonstrate a wide variation in the organization of care – generally lacking centralization, and the physicians' acknowledgement of insufficient knowledge on the management of pregnant women with cancer. There is a need for improvement through national centralization and/or establishing advisory boards for cancer in pregnancy. Seeing the paucity of cancer in pregnancy experience, the importance of global multidisciplinary collaboration is emphasized.

INTRODUCTION

The incidence of cancer in women of reproductive age is increasing, with age-standardized incidence rates rising from 180 to approximately 200 per 100 000 women between the age of 20-49 over the past 20 years [1,2]. As maternal age at delivery continues to increase the incidence of cancer during pregnancy continues to rise [3,4]. The expected number of pregnancies worldwide is around 213 million each year [5]. It is estimated that approximately one in 2000 pregnancies is complicated by cancer, resulting in around 106.500 pregnant women being confronted with a cancer diagnosis each year globally [6,7]. In Europe this would add up to approximately 2 000 pregnant women and with an estimate of more than 10 000 oncologists in Europe, each specialist will only see less than one pregnant woman with cancer in a 5-year period[8]. This emphasizes the low exposure of physicians to this specific patient population. Taking into account that there are approximately 70 000 obstetricians and gynecologists in Europe, their exposure to pregnant patients with cancer will be even lower [9]. The variety of cancers that can appear during pregnancy at different gestational ages confers a multidisciplinary challenge, further decreasing the possibility of a treating physician becoming experienced in the management of those diverse clinical situations.

For the above-mentioned reasons, there is a noticeable heterogeneity in both oncologic and obstetrical management for pregnant women worldwide [10]. To minimize the level of substandard care for this group of women, it is important to share expertise and centralize care as much as possible. This increase in expertise and centralization of care may offer the benefit of less delay of oncologic treatment and may prevent unnecessary preterm deliveries. Over the last decade, several initiatives have been launched to achieve this goal [11-13]. The International Network on Cancer, Infertility and Pregnancy (INCIP) has investigated this group of patients extensively over the past decades, to improve knowledge and by that, care for these women. To apply this knowledge to clinical care, multidisciplinary advisory boards have been launched over the last years, including the Dutch mail-based advisory board 'Adviesgroep Kanker en Zwangerschap'[12], the French mail-based national advisory board 'Cancer Associé à La Grossesse', the Serbian 'Tumor Board for Cancer and Human Reproduction', and the international 'Advisory Board on Cancer, Infertility and Pregnancy' (ABCIP) [11]. These initiatives are not implemented everywhere yet and they are mainly known by the experts in the field and their colleagues. Next to that, it is unknown to the authors to what extent national guidelines exist on the management of cancer during pregnancy. To evaluate the experience with cancer in pregnancy and to obtain insight in the local organization of care and gaps in knowledge in this commentary, the results of a survey sent to colleagues around the world were gathered, to serve as a basis for the development of future global initiatives to improve the organization of care and identify gaps in knowledge.

SURVEY

The three focus points of our survey were: 1) clinical experience with pregnant women with cancer (on a personal and hospital level), 2) the organization of care at the different levels, and 3) current gaps in knowledge. Full survey can be found in the ***supplementary appendix***. The survey was distributed through various networks of the INCIP and ABCIP members and several professional societies around the world, and by contacting authors of articles related to cancer in pregnancy. A total of 246 responses from participants in 36 countries were obtained, with most responses coming from European and American countries, probably because most of the networks used do not yet reach physicians from African and Asian countries. The described findings and interpretations can therefore not be generalized to those parts of the world. The geographic distribution and percentage per discipline of the participants are shown in ***Figures 1 and 2***. The majority of physicians worked in an academic center (n=181; 73%). Furthermore, 66 (27%) respondents are active members of the INCIP organization.

CLINICAL EXPERIENCE WITH PREGNANT WOMEN WITH CANCER

The experience with cancer in pregnant patients differed widely between the physicians answering our survey, as can be seen in ***Figure 3***. On a hospital level, 58% of the physicians responded that in their center less than 10 patients with cancer during pregnancy are treated each year (n=144), in 21% (n=51) 10-20 patients are treated, and in 6% (n=15) more than 20 patients per year. More than half of the respondents mentioned the lack of centralized care in their country and 71% of the physicians refer their pregnant women with cancer by default to a multidisciplinary team in cancer centers.

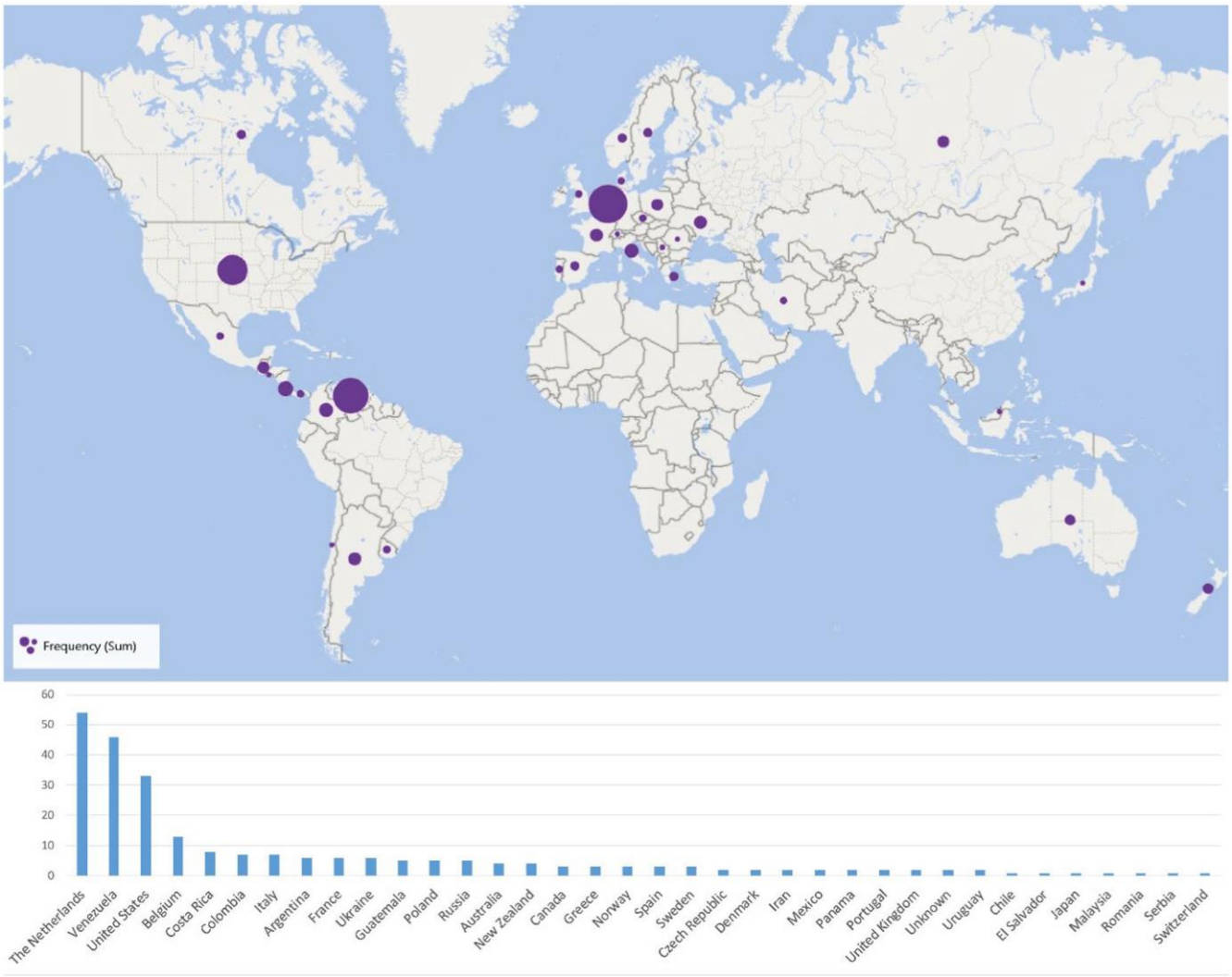


Figure 1. Frequency and location of respondents per country. The map shows an overview of amount of respondents per country, with the size of the dot corresponding to the amount of respondents, as shown in the bar chart below.

This shows that individual experience with pregnant women with cancer is very low, even in physicians collaborating in international networks such as the INCIP; thus that cancer during pregnancy should be regarded as a rare disease. Rare diseases are, based on official WHO criteria, defined as diseases with an incidence of 1 per 2 000 people [14]. Although cancer during pregnancy cannot be officially defined as a rare disease because it consists of a variety of cancer diagnoses, the incidence is similarly low and patients in this unique situation encounter the same problems as patients and physicians confronted with rare diseases[15]. Guidelines defining requirements for specialized care in order to pursue optimal care for patients with rare cancer are increasingly being developed by European Reference Networks [16]. One of the requirements mentioned in these guidelines is a minimum number of patients with a specific malignancy per center (for less common malignancies a minimum of 10 per year) [17]. According to this survey outcomes, the majority of physicians mentioned that in their

hospitals less than 10 pregnant women with cancer are treated each year. To provide sufficient specialized care to this specific group of patients, referrals to a specialized regional or national hospital or communication with experts on this topic is necessary to improve patient outcomes.

ORGANIZATIONS OF CARE

MDTs and specific advisory boards

Of all physicians answering our survey, 61% (n=153) responded that their pregnant patients with cancer are being discussed in multidisciplinary oncological teams (MDTs) in their hospital. Regional MDTs discussing these patients were mentioned by 21% (n=53) of the physicians, and 23% (n=58) mentioned MDTs on a national level. A specific national multidisciplinary advisory board discussing cancer in pregnancy, with oncological as well as obstetrical and neonatal disciplines, operating in their country was mentioned by 35% of physicians (n=87) from 12 countries.

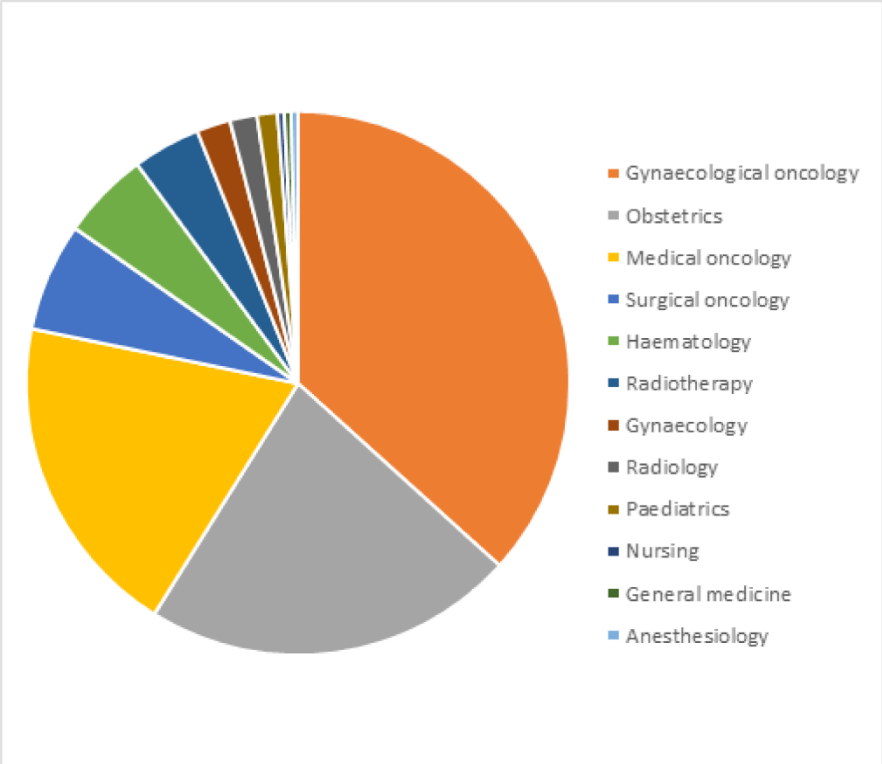


Figure 2. Distribution of respondents per discipline.

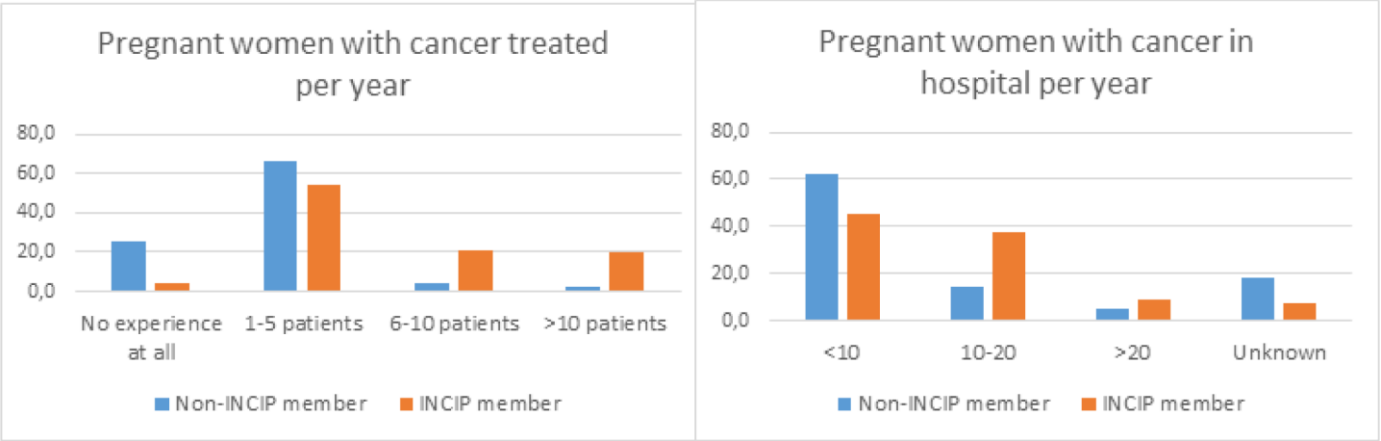


Figure 3. Bar plot showing the percentage of respondents per category. (A) Distribution of amount of CIP patients that are treated per year and (B) number of CIP patients that are treated in their hospital per year

This survey showed promising results with regard to the accessibility of experts in the field of cancer in pregnancy on a national level, with a majority of physicians mentioned they always consult an expert in case of a pregnant woman with cancer (59%; n=148). But still, almost 10% of physicians mentioned they do not know the experts in their country and 64% of all physicians mention a further need for easily accessible consultation of experts in the field of cancer and pregnancy. Following the previously mentioned lack of specialized hospitals on a national level, easily accessible consultation of experts can potentially improve up-to-date knowledge of cancer in pregnancy and treatment plans on a hospital level. International advisory boards, like the ABCIP (www.ab-cip.org), may offer a solution [11,12]. Expanding the already existing national advisory boards working on the ABCIP platform to more countries, and including more physicians from different countries in the overarching international advisory board will increase their visibility and help more physicians with questions regarding their pregnant women with cancer. Expanding the utilities of a platform such as the ABCIP by including guidelines, evidence-based knowledge and information on national and international initiatives regarding cancer in pregnancy might also improve the care for this group of women.

Registration of pregnant women with cancer

Registration of pregnant women with cancer can help fill the gaps in knowledge. However, registration may vary widely. The outcomes of this survey show that 15% (n=38) of all physicians mentioned they do not register their pregnant cancer patients anywhere, whereas 25% (n=63) mentioned they only register them in general national tumor registry. Local registration of pregnant women with cancer was noted by 17% (n=42) of all physicians, regional registration by 11% (n=27), national registration by 27 % (n=68) and international registration by 15% (n=37); 17% (n=41) of the respondents did not know whether there was any registration at all. Grouping responses per country showed that 13

of the 36 countries (36%) have a national registration of patients. A structured follow-up of the children born after in-utero exposure to cancer treatment of the mother was mentioned by 31% (n=77) of all physicians.

CURRENT GAPS IN KNOWLEDGE

The survey involved one open-answer question where physicians could list what they considered the most important gaps in knowledge about cancer in pregnancy. This question was answered by 131 of the 246 respondents. The most important knowledge gaps are shown in ***Table 1.***

Novel therapy options like targeted molecular agents and immunotherapy during pregnancy (n=36)
Coordination of care and international collaboration (n=26)
Guidelines and core outcome sets (n=15)
Long-term outcomes of children in utero exposure to cancer (therapy) (n=13)
The risk of diagnostic imaging and radiation therapy during pregnancy (n=10)
Psychological and peer support (n=9)
Specific knowledge on gynecological malignancies during pregnancy (n=5)
Possible influences of pregnancy on cancer and treatment (n=5)

Table 1. Current gaps in knowledge.

Half of the physicians responding to the survey mentioned gaps mostly regarding novel therapeutic options and knowledge of treatment of specific tumor types during pregnancy. This interest in novel therapeutic options during pregnancy is already being translated to an increase in research on novel treatment modalities during pregnancy, such as immunotherapy, targeted therapy, and proton therapy [18-20]. With increasing literature on oncological treatment options during pregnancy, increasing numbers of patients are being treated during pregnancy, including with chemotherapy. Sixteen respondents specifically mentioned the differences in knowledge between expert centers and non-expert centers and the need for multidisciplinary consultation and medical training regarding this specific patient population. It is necessary to register these patients in (inter)national registries and report on the outcomes, especially the (long-term) outcomes of the children, to underscore further the safety of specific treatment regimens, and discover the specific risks and precautions that need to be

taken. Although educational resources to address the gaps that were identified were not specifically examined, it seems reasonable to conclude that discussions of pregnancy care should be widely incorporated into training program curricula, continuing medical education activities, and educational sessions at oncology and obstetric society meetings. This should include the dissemination of information on already available resources for physicians treating these patients.

Furthermore, respondents mentioned the missing focus on psychological and peer support needed with this impactful coincidence of cancer and pregnancy. Literature on the psychological aspects of a cancer diagnosis during pregnancy is increasing. Vandenbroucke et al. identified the risks of pregnant women with cancer and their partners for high levels of distress based on their coping profiles and already concluded that specifically those women and partners that used internalizing coping strategies might benefit from additional psychosocial support [21]. A systematic review performed by Leung et al. concluded that women with gestational cancer experience psychological distress associated with concerns about their babies' health and Matsuo et al. showed that pregnant women with a malignancy were 49% more likely to have a diagnosis of anxiety or depressive disorder compared with pregnant women without a malignancy [22,23]. The outcomes of this survey might indicate that interest in this specific topic is increasing, but the literature might not yet be known by physicians working with pregnant women with cancer.

Our survey yielded insights into the significant variation in the organization of care for pregnant women with cancer worldwide. The main strength of the survey was the large number of respondents from a wide range of countries and disciplines around the world, contributing to obtaining an overall view from physicians who treat pregnant patients with cancer, as well as getting insight into the organization of care and current gaps in knowledge. It should be noted that since this survey was a register of current clinical practices of a rare situation, it was not officially validated. Therefore, the possibility of misinterpretation of questions by some of the respondents must be taken into account, although a large number of respondents probably has minimized this effect. The use of merely categorical or dichotomous answers helped us to interpret the responses, but may have introduced some form of bias or limitation in the respondents' responses. The questionnaire was sent out mainly with help from members of the INCIP and ABCIP. This may have influenced the outcomes of the questionnaire since many members are seen as experts on cancer during pregnancy by their network. The results of this questionnaire might be an overestimation of nationwide knowledge and current clinical practice on a regional level. On the other hand, only a minority of respondents were INCIP members and even with a possible overestimation of knowledge, the need for a more structured organization of care was acknowledged by many of them.

CONCLUSION

Although evidence of appropriate approaches to diagnostic options, treatment and follow-up of pregnant women with cancer is increasing, the outcomes of the survey sent out by us show that there are still significant variations in the organization of care for women with cancer during pregnancy. More information and easier access to experts, for example through centralization of care where possible and online advisory boards such as the ABCIP, as well as increased national and international collaboration, should improve overall care for this rare patient group in the future.

REFERENCES

1 Sung, H. *et al.* Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. *CA Cancer J Clin* **71**, 209-249 (2021).

2 Ward, E. M. *et al.* Annual Report to the Nation on the Status of Cancer, Featuring Cancer in Men and Women Age 20-49 Years. *J Natl Cancer Inst* **111**, 1279-1297 (2019).

3 Matthews, T. J. & Hamilton, B. E. Delayed childbearing: more women are having their first child later in life. *NCHS Data Brief*, 1-8 (2009).

4 *National Institute for Health and Welfare. Nordic perinatal statistics 2014. Helsinki, Finland. Available at: https://www.thl.fi/en/web/thlfi-en/statistics/statistics-by-topic/sexual-and-reproductive-health/parturients-deliveries-and-births/nordic-perinatal-statistics . (Accessed Nov 9th, 2022)*.

5 Sedgh, G., Singh, S. & Hussain, R. Intended and unintended pregnancies worldwide in 2012 and recent trends. *Stud Fam Plann* **45**, 301-314 (2014).

6 Smith, L. H., Danielsen, B., Allen, M. E. & Cress, R. Cancer associated with obstetric delivery: results of linkage with the California cancer registry. *Am J Obstet Gynecol* **189**, 1128-1135 (2003).

7 Stensheim, H., Møller, B., Van Dijk, T. & D., F. S. Cause-specific survival for women diagnosed with cancer during pregnancy or lactation: A registry-based cohort study. *Journal of Clinical Oncology* **27**, 45-51 (2009).

8 de Azambuja, E. *et al.* The landscape of medical oncology in Europe by 2020. *Ann Oncol* **25**, 525-528 (2014).

9 *OECD (2022), "Health care resources", OECD Health Statistics (database),(accessed Nov 28th 2022).*

10 de Haan, J. *et al.* Oncological management and obstetric and neonatal outcomes for women diagnosed with cancer during pregnancy: a 20-year international cohort study of 1170 patients. *The Lancet Oncology* **19**, 337-346 (2018).

11 Amant, F., Heimovaara, J. H., Lok, C. A. R. & Van Calsteren, K. The Advisory Board on Cancer, Infertility and Pregnancy: a virtual on-demand multidisciplinary tumour board. *The Lancet Oncology* (2022).

12 Heimovaara, J. H. *et al.* Ten-year experience of a national multidisciplinary tumour board for cancer and pregnancy in the Netherlands. *Eur J Cancer* **171**, 13-21 (2022).

13 Maggen, C. *et al.* Pregnancy and Cancer: the INCIP Project. *Curr Oncol Rep* **22**, 17 (2020).

14 World Health Organization. *Priority diseases and reasons for inclusion - Rare diseases*. https://www.who.int/medicines/area/priority_medicines/Ch6_19Rare.pdf (accessed Jan 27th 2021)

15 Lok, C. & Amant, F. Editorial: The challenge of treating and investigating rare gynaecologic cancers. *Curr Opin Oncol* **33**, 432-434 (2021).

16 European Commission. European Reference Networks (ERNs), European Union. Available at: https://ec.europa.eu/health/ern_en (Accessed Dec 22th 2022).

17 Stichting Oncologische Samenwerking (SONCOS). SONCOS Normeringsrapport - versie 10 (2018). https://demedischspecialist.nl/normeringsrapport-van-soncos (accessed Dec 16th 2022).

18 Borgers, J. S. W. *et al.* Immunotherapy for cancer treatment during pregnancy. *The Lancet. Oncology* **22**, e550-e561 (2021).

19 Lambertini, M., Peccatori, F. A. & Azim, H. A., Jr. Targeted agents for cancer treatment during pregnancy. *Cancer treatment reviews* **41**, 301-309 (2015).

20 Heimovaara, J. H. *et al.* Proton therapy of a pregnant patient with nasopharyngeal carcinoma. *Clin Transl Radiat Oncol* **35**, 33-36 (2022).

21 Vandenbroucke, T. *et al.* Psychological distress and cognitive coping in pregnant women diagnosed with cancer and their partners. *Psycho-Oncology* (2017).
22 Leung, V., Bryant, C. & Stafford, L. Psychological aspects of gestational cancer: A systematic review. *Psychooncology* **29**, 1734-1745 (2020).
23 Matsuo, K. *et al.* Prevalence of anxiety and depressive disorders in pregnant women with malignancy. *Int J Gynaecol Obstet* **160**, 635-640 (2023).

Chapter 5 Ten-year experience of a national multidisciplinary tumour board for cancer and pregnancy in the Netherlands

Joosje Heimovaara, Ingrid Boere, Jorine de Haan, Kristel Van Calsteren, Frédéric Amant, Lia van Zuylen, Christianne Lok

European Journal of Cancer, May 2022

ABSTRACT

Background Most physicians encounter pregnant women with cancer incidentally, leading to lack of expertise or confidence to inform and treat these patients based on the most recent guidelines and expert opinions. In the Netherlands, a national multidisciplinary tumour board for cancer, infertility and pregnancy (CIP-MDT) was founded in December 2012 including 35 specialists from a variety of disciplines. This study evaluates the frequency of consultation of the CIP-MDT, the types of questions asked and the satisfaction of consulting physicians with its existence.

Methodology Of all requests to the CIP-MDT between December 2012 and June 2021, tumour type, stage, gestational age at diagnosis and recommendations were collected and analysed. For evaluating the methods of the CIP-MDT, a survey with questions regarding experiences with the CIP-MDT and impact on treatment decisions was sent out to physicians that consulted the CIP-MDT.

Results Recommendations (n=213) concerned preferred and safest options for imaging, treatment options during pregnancy, possible effects on child and fertility preserving options. Most frequently discussed malignancies were breast cancer (n=66), cervical cancer (n=34), haematological malignancies (n= 32) and melanoma (n=21). The questionnaire was completed by 54% of the physicians (n=50). Satisfaction with the recommendations of the CIP-MDT was high and 94% of the physicians informed their patients about consulting the CIP-MDT and felt supported by the received recommendations.

Discussion The national Dutch CIP-MDT contributes to a high level of satisfaction among physicians requesting advice. Further research should be executed to confirm that a CIP-MDT improves the outcomes for pregnant women and their children.

INTRODUCTION

Although cancer in pregnancy affects more than 2000–4000 women in Europe each year, individual physicians encounter this situation infrequently.[1] Therefore, many physicians lack the expertise and confidence to treat pregnant women with cancer according to the most recent insights. Pooling, reviewing and analyzing cases of multiple patients with cancer during pregnancy will increase the expertise.. This leads to suboptimal care, both oncological and obstetrical.[2] A national multidisciplinary tumour board (MDT) for cancer, infertility and pregnancy (CIP-MDT) could contribute to improved care for these patients.

MDTs are part of standard oncological care, assuring multidisciplinary treatment according to the best available evidence or multidisciplinary consensus.[3] The establishment of CIP-MDTs in every hospital providing oncological care is not realistic due to low patient numbers. Geographical and logistic barriers can hinder the referral of these patients to hospitals with dedicated CIP-MDTs. Finding alternative ways to provide the most optimal care to these patients is therefore highly relevant.

In the Netherlands, a national CIP-MDT, 'Adviesgroep Kanker en Zwangerschap', was founded in December 2012 to support Dutch physicians with treatment decisions regarding their pregnant patients with cancer. This CIP-MDT consists of specialists of varying disciplines (Table 1). Physicians requesting advice are asked to send a (anonymous) summary of the obstetrical and oncological medical history of their patient together with their routine cancer treatment proposal for a non-pregnant patient. The CIP-MDT formulates written recommendations on how and if standard treatment is possible in relation to the pregnancy, with any obstetrical adjustments or precautions.

This study evaluates how often a CIP-MDT is consulted, whether this has changed over the year, the recommendations given, and evaluates feedback on the working methods of the MDT and the satisfaction of the physician requesting advice.

MATERIAL AND METHODS

Summary of cases

All patients discussed in the CIP-MDT were anonymously registered in a database. The recommendation letters were gathered. Data on tumour type and stage, trimester at diagnosis, type of request and final recommendations were extracted. Data were retrieved from August 2013 until June 2021. In

some cases, the documented recommendation was not available since the requests required immediate response by mail or phone, due to urgency of the request. Figure 1 shows the routine handling of requests by the CIP-MDT.

Questionnaire

In October 2020, a questionnaire was sent out to 93 Dutch physicians, who requested one or more recommendations from the CIP-MDT between August 2013 and October 2020, even when no formal recommendation letter was available. SurveyMonkey (www.surveymonkey.com) was used for distribution of questionnaires and collection of data. Reminders were sent three and five weeks after first invitation. The questionnaire contained 28 questions regarding accessibility of the CIP-MDT, recommendations received and their impact on treatment decisions (Appendix). There were 17 multiple-choice questions, seven 1 to 10 scale questions (from 'strongly disagree' to 'strongly agree') and four open-end questions. Informed consent was obtained from all participating physicians. Since this is not an interventional study according to Dutch law, formal ethical approval was waived by the Ethical review board of the Netherlands Cancer Institute.

Medical specialists
Anesthesiologist
Clinical pharmacologist
Ethical advisor
Medical physicist
Fertility specialist
Gynecologic oncologist
Hematologist
Medical oncologist
Obstetrician
Oncological physicist
Pediatric oncologist
Radiation oncologist
Radiologist
Surgical oncologist

Table 1. Disciplines represented by the CIP-MDT

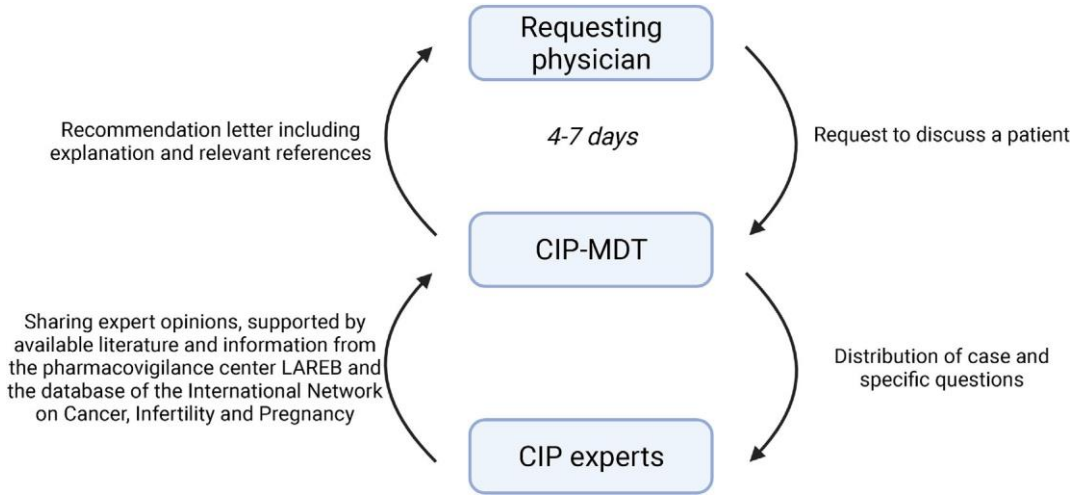


Figure 1. Workflow of the CIP-MDT. Requests to discuss a patient in the CIP-MDT and to formulate a recommendation were received by e- mail. Patient data were anonymized and distributed by e-mail in standardized format among all members of the CIP-MDT along with specific questions of the treating physician. All medical experts of the CIP-MDT contributed to the conversation by mail in their area of expertise. The discussion continued until a uniform, tailor made recommendation letter could be formulated. Beside expert opinion, the recommendations were supported by available literature, by data from the Dutch pharmacovigilance center LAREB and by additional data of similar patients in the database of the International Network on Cancer, Infertility and Pregnancy (INCIP).[35] The letter containing the formulated recommendation including the explanation and relevant references, was sent to the requesting physician usually within four to seven days after the request was received. When needed, urgent on-demand recommendations can be provided.

Data were analysed in IBM SPSS Statistics (version 25). Standardized descriptive analyses were used with medians, percentages and ranges (0-10). Subgroups of different tumour types were analysed for stage, subtype of cancer and type of initial treatment. Gestational age was categorized in weeks and trimester. An independent samples t-test was performed to compare the number of times different types of requests were asked of the advisory board in the first five years compared to the last five years.

RESULTS

From August 2013 until June 2021, 213 recommendation letters were formulated for 119 requesting physicians from 42 different hospitals (Supplementary figure 1). Number of requests increased from two in 2013 to 44 in 2020 (Figure 2). Questions concerned cancer during and after pregnancy or were related to fertility (Table 2). The vast majority regarded breast cancer (n=65, 30.5%), followed by cervical cancer (n=35, 16.4%), haematological malignancies (n=32, 15.0%) or melanoma (n=21, 9.9%). 141 (81.1%) of all pregnant patients were in their 2nd or 3rd trimester of pregnancy at time of advice request. Content of recommendations is summarized in figure 3. When comparing the types of requests asked in the first five years of existence compared to the last five years overall, a decrease in percentages was seen of all types of requests except treatment during delivery and timing or modus of delivery

(Table 3). Of all percentages of types of requests that decreased, which 4 were significantly lower between 2017-2021, as shown in table 3.

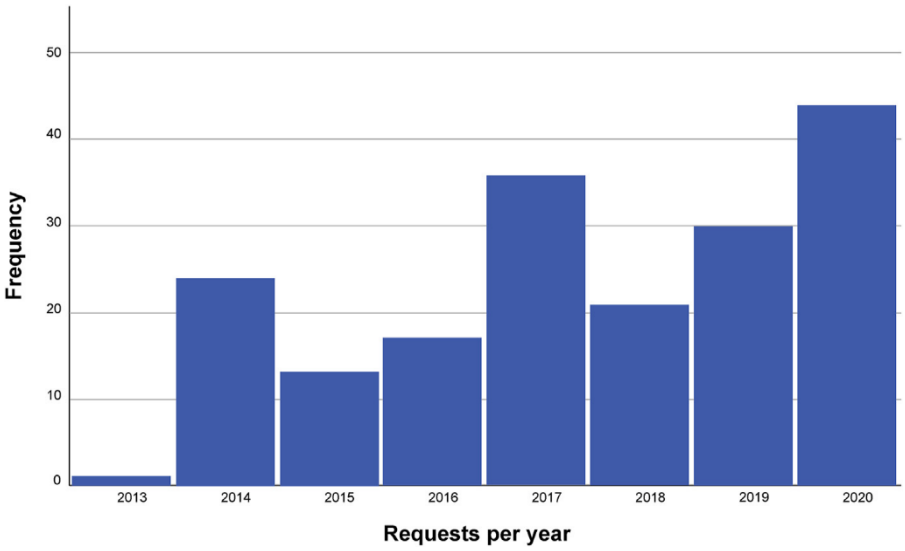


Figure 2. Amount of requests discussed by the CIP-MDT per year (2013-2020).

TOTAL NUMBER OF PATIENTS	213
Cancer type	
Breast cancer	66 (31.0%)
Cervical cancer	34 (16.0%)
Hematological Cancer	32 (15.0%)
Melanoma	21 (9.9%)
Ovarian cancer	11 (5.2%)
Sarcoma	9 (4.2%)
Brain tumor	8 (3.8%)
Thyroid cancer	4 (1.9%)
Urothelial cell carcinoma	3 (1.4%)
Gastric cancer	3 (1.4%)
Colon carcinoma	3 (1.4%)
Neuro-endocrine tumor	2 (0.9%)
Lung cancer	2 (0.9%)
Rectal carcinoma	2 (0.9%)
Vulvar carcinoma	2 (0.9%)
Other	11 (5.2%)
Type of request	
Cancer during pregnancy	174 (81.7%)
Preconception	23 (10.8%)
Pregnancy after cancer (treatment)	13 (6.1%)
Postpartum cancer diagnosis	1 (0.5%)
Cancer of the fetus	1 (0.5%)
Cancer treatment of father during conception	1 (0.5%)
Trimester at time of request	174
1st	33 (19.0%)
2nd	80 (46.0%)
3rd	61 (35.1%)
Metastatic disease	20 (9.4%)
Recurrent disease	14 (6.6%)
Only pain relief and supportive care during pregnancy	4 (1.9%)

Table 2. Overview of cases discussed in the CIP-MDT.

Breast cancer

Of 65 breast cancer patients, 53 (81.5%) had their diagnosis during pregnancy, nine (13.8%) wished to conceive after cancer(treatment) and three (4.6%) were pregnant shortly after cancer(treatment). Stages of disease varied. Of 50 patients with a registered hormone receptor status, breast cancer was triple negative in 20 (40%), ER and/or PR positive and HER2NEU negative in 16 (32%) and triple positive in 10 (20%) patients. The content of requests is outlined in Figure 3.

Information on starting and/or sequence of therapy mostly concerned questions whether to start with surgery or neo-adjuvant chemotherapy. The CIP-MDT considered chemotherapy as optimal therapy during pregnancy in 31 (67.4%) patients, after at least 12 weeks of gestation, ending before 36 weeks of pregnancy.[4, 5] Surgery during pregnancy was recommended for 20 (43.5%) patients.[6] When a sentinel node procedure was part of the proposed treatment plan, it was recommended to perform this without blue dye, due to the possibility of an anaphylactic reaction of the mother.[7] For nine pregnant patients (20.5%), radiation therapy was part of the proposed treatment plan. Of the 37 documented recommendations regarding treatment during pregnancy, 12 (32.4%) did not follow standard protocols for non-pregnant patients, mostly because the CIP-MDT advised against hormonal and HER2NEU targeted therapy in pregnancy. Six patients were diagnosed with distant metastases, including four with a recurrence. For these patients, recommendations were requested regarding options for pain relief and radiation therapy for metastatic lesions, or delivery options in the presence of vertebral or pelvic metastases. For patients with early pregnancies and/or poor prognosis, termination of pregnancy was considered. It was only recommended if the pregnancy was discovered after diagnostic imaging and/or adjuvant radiation therapy resulting in very high fetal radiation dose leading to a significant risk of congenital abnormalities. Requests regarding women with active intention to conceive mostly concerned premature interruption of hormonal therapy and preconception questions in patients with a poor prognosis.

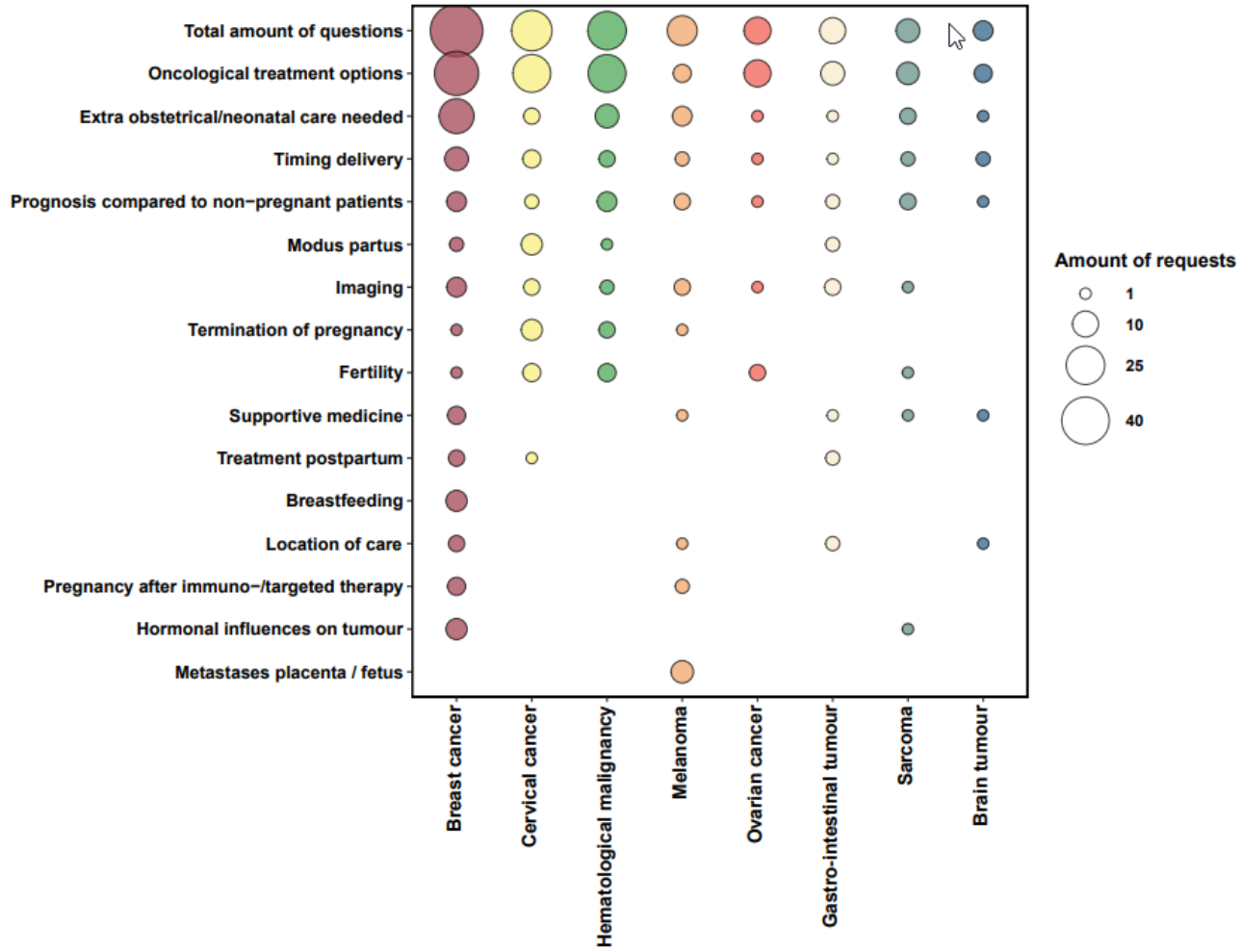


Figure 3. Types of requests asked per tumour type. Bubble chart shows the amount of times different types of requests were asked per tumour type. First row shows maximum amount of times requests were asked. Some requests concerned several questions, these are all scored separately

	TIMEFRAME			
	2012-2016	2017-2020	Difference	p-values
	n = 33	n = 134		
ONCOLOGICAL TREATMENT OPTIONS	69.7	79.1	+9.4%	0.251
EXTRA OBSTETRICAL/NEONATAL CARE NEEDED	54.5	20.1	-34.4	<0.001
TIMING DELIVERY	9.1	14.9	+5.8%	0.387
PROGNOSIS COMPARED TO NON-PREGNANT PATIENTS	21.2	5.2	-16.0%	0.003
MODUS PARTUS	6.1	7.5	+1.4%	0.782
IMAGING	18.2	9.7	-8.5%	0.171
TERMINATION OF PREGNANCY	12	5.2	-6.8%	0.154
FERTILITY RELATED QUESTIONS	9.1	4.5	-4.6%	0.296
SUPPORTIVE MEDICINE	0	5.2	+5.2%	0.182
TREATMENT POSTPARTUM	6.1	3	-3.1%	0.398
BREASTFEEDING	12.1	1.5	-10.6%	0.003
LOCATION OF CARE	6.1	3.7	-2.4%	0.553
PREGNANCY AFTER IMMUNO/TARGETED THERAPY	6.1	3	-3.1%	0.398
HORMONAL INFLUENCES ON TUMOUR	27.3	4.5	-22.8%	<0.001
METASTASES PLACENTA/FETUS	6.1	3.7	-2.4%	0.553

Table 3. Types of requests asked per time frame. *Percentage of times types of requests were asked during the first five years of existence of the advisory board (2012-2016, n=33) and the second (2017-2020, n=134)*

Cervical cancer

Recommendations were requested for 34 patients with cervical cancer. Of 26 patients with known stage of disease, 12 (46.2%) were diagnosed with FIGO stage IB during pregnancy, six (23.1%) with stage IIB, three (11.1%) with stage IA1, two (7.7%) with stage III, two (7.7%) with stage IV and one with stage IIA (3.8%).

Treatment of cervical cancer during pregnancy is difficult since standard treatment is often not compatible with ongoing pregnancy. For seven patients (25.8%) with early stage disease, conisation and/or lymphadenectomy (during early pregnancy) was recommended.[8] For higher stages the majority of requests concerned the possibility of preserving the pregnancy, the possibility of postponing definitive treatment until after delivery, and the mode of delivery (Figure 3). Preservation of pregnancy was possible in 24 patients (80%). Chemotherapy during pregnancy was recommended for 17 patients (54.8%), with possible further treatment postponed until after delivery. To avoid previable termination, in four patients up to six cycles of chemotherapy were needed. To avoid the slight possibility of tumour spill during vaginal birth with possible metastasis in a vaginal or perineal tear, episiotomy site or even to the child, the CIP-MDT recommended a caesarean section in all cases.[9-11]

For seven (35%) patients with stage IIB or IIIC (FIGO 2018) diagnosed prior to 24 weeks of gestation, termination of pregnancy was recommended to avoid suboptimal treatment.[12] In most of these cases chemoradiotherapy was proposed, making fetal death inevitable.

Haematological malignancies

Of 32 patients with haematological malignancies, 27 (84.4%) had a malignancy during pregnancy, three (9.4%) patients were diagnosed postpartum and two (6.3%) wanted to conceive after haematological treatment. Twelve (37.5%) patients had acute myeloid leukemia, including three acute promyelocytic leukemia, three (9.4%) had acute lymphoblastic leukemia, three (9.4%) chronic myeloid leukemia, eight (25.0%) non-Hodgkin lymphoma and six (18.8%) Hodgkin lymphoma.

Most requests were concerned with advice on haematological treatment options during pregnancy (Figure 3), due to toxicity of most standard chemotherapy regimens for haematological malignancies and the lack of cancer treatment experience during pregnancy.[13-16] Of 21 cases with documented recommendations regarding treatment during pregnancy, 10 (47.6%) deviated from the standard protocol for non-pregnant patients. The CIP-MDT supported proposed termination of pregnancy in four (12.5%) cases due to a stem cell transplantation or intensive chemotherapy needed during early pregnancy, both not compatible with a viable fetus.

Melanoma

Of thirteen requests concerning patients with a melanoma during pregnancy, four wished to conceive after melanoma treatment, three were pregnant after previous melanoma treatment including immunotherapy and one was diagnosed postpartum.

Recommendations were mostly sought regarding the possibility of placental and fetal metastases, and whether extra obstetrical precautions would be necessary (Figure 3). Information on whether pregnancy would increase the risk of recurrence, or consequences of immunotherapy on a future pregnancy was also requested. The CIP-MDT recommended to delay conception at least six months after treatment, based on biological aspects of the tumour and targeted- and immunotherapeutic agents, case reports and available literature.[17] Surgery during pregnancy was recommended for 83.3%, e.g. (re-)excision of the tumour and/or sentinel node procedure (with Technetium-99 and avoiding blue dye).[7] The CIP-MDT recommended perfoming histologic examination of the placentas, due to the increased risk of placental metastasis in melanoma patients, especially in the case of metastatic dis-

ease.[18] Diagnostic imaging, including fluorine-18-flurodeoxyglucose positron emission tomography integrated with computed tomography was considered feasible for three patients when necessary for treatment planning, since the radiation dose is far below the threshold for fetal damage.[19]

Rare cancers

Based on the rare disease definition of the European RARECARE project (less than six per 100 000 per year), 52 of all requests (24.4%) concerned rare cancers.[20] Most requests regarded patients with sarcoma (n=9) and brain tumours (n=7) (Table 2). The CIP-MDT advised caution with temozolomide administration during pregnancy for brain tumour cases, because of unknown effects on the fetus and increased risk of severe thrombocytopenia.[21-23] Cerebral radiation therapy during pregnancy was considered to be safe, since the distance from the uterus to the irradiation area remains large enough throughout the whole pregnancy.[21]

Additional recommendations

Furthermore, for all cases discussed, not only the consequences of primary oncological medication itself were considered, but also issues as supportive drugs, location of care and obstetrical precautions during surgery or labor and delivery (Figure 3). Based on these frequently asked questions the CIP-MDT received, default texts were formulated. The CIP-MDT always recommended monitoring fetal growth by ultrasound biometry when systemic therapy is administered and attached supplementary information on obstetrical care to the recommendation letter. Also, it pointed out to focus on the psychological support for pregnant women with cancer and their family and recommended follow-up of the children after birth.[24]

Questionnaire

The questionnaire was answered by 50 physicians (54%). Two-third of all responding physicians worked in an academic hospital or oncology center and one third in a general hospital. Most respondents were gynecologist (n=28, 56%). The average number of requests per physician was 2, 12 and 27 respondents (56%) contacted the CIP-MTD multiple times, with the maximum of six times by four respondents. Recommendations were received within a week in 96% of the cases. Overall satisfaction with the recommendations and way of communication was high, with a mean of 8.29 on a scale from 1-10 (SD= 2.064), leading to a large number of physicians basing their final treatment plan on the recommendations (M=8.85, SD=1.946) (Supplementary figure 2). Almost all physicians (94%) informed their patients about consulting the CIP-MDT, felt supported by the received recommendations and would recommend the CIP-MDT to their colleagues.

DISCUSSION

This study shows that a national CIP-MDT for cancer during pregnancy is regularly consulted and the number of requests increases with time. The CIP-MDT is highly appreciated by physicians and repeat consultation often occurs. However, the percentage of patients discussed in the CIP-MDT is only a fraction of the total number of pregnant women affected by a diagnosis of cancer and the physicians who may be treating them. The incidence of cancer during pregnancy is estimated to be 1 in 1000-2000 live births. With approximately 170 000 live births annually in the Netherlands, close to 170 pregnant women are diagnosed with cancer annually.[25-28] In 2020, 25% of these patients were discussed in the nation CIP-MDT. Whether this is explained by unfamiliarity with the CIP-MDT or that treatment was provided by physicians with experience in treating pregnant patients with cancer is unclear. The increase of requests over the years suggests the first.

The change in percentages for the different types of questions in the last 5 years could indicate that more treatment is started during pregnancy leading to more questions on treatment options and timing of delivery and less questions on termination of pregnancy. This trend in more treatment during pregnancy can be a sign of increased knowledge on the often similar prognosis during pregnancy and which obstetrical and neonatal care is necessary. Another explanation would be that more women are referred to physicians with experience in providing the obstetrical care for the patient population, but further documentation of advice requests and recommendations in the figure could show whether this changed in percentages is only incidentally or remains.

The malignancies discussed in the CIP-MDT reflect the expected incidence in pregnancy.[29] When taking into account all types of malignancies occurring at different gestational ages, most physicians lack the opportunity to acquire enough experience with pregnancy-related malignancies. Exposure of a medical specialist to a rare health problem is related to knowledge and quality of care and is of great importance for the outcome of the patient.[30] A nationwide CIP-MDT increases exposure and thus experience of members, building sufficient knowledge and supporting colleagues throughout the country to treat and care for mother and child as close to home as possible. Board members of the CIP-MDT have gained experience in determining the feasible treatment options during pregnancy but also the safest way of treatment for mother and child in the absence of evidence-based guidelines. This experience is based on the review and pooled analysis of the outcomes of a larger number of patients with cancer in pregnancy.

Although cancer during pregnancy does not meet the official WHO criteria of a rare disease, this unique situation raises similar issues.[20, 31, 32] These include the small number of patients spread over a country,

logistic problems to reach expert centers, lack of validated diagnostic tools and treatments, limited clinical expertise and lack of evidence based guidelines. Dedicated guidelines for the specialized treatment of different medical conditions are increasingly developed to optimize patient care, but have not yet been published for all the different types of cancer encountered during pregnancy. However, no hospital could fulfill all these requirements. Membership of a national CIP-MDT and (inter)national registration can resolve this problem.

Figure 4 shows the steps necessary to establish a CIP-MDT. Enthusiasm of stakeholders to participate in an on demand virtual CIP-MDT, will ultimately determine its success and sustainability. The variety of questions received by the CIP-MDT underlines the importance to include experts of various disciplines. Agreements must be made concerning means of communication of the CIP-MDT, how to be contacted by requesting physicians, timing of response, formation of the board, planning of regular meetings. Visibility is key to success and acknowledgement of national medical societies and a yearly conference can be a next step in achieving this.[33, 34]

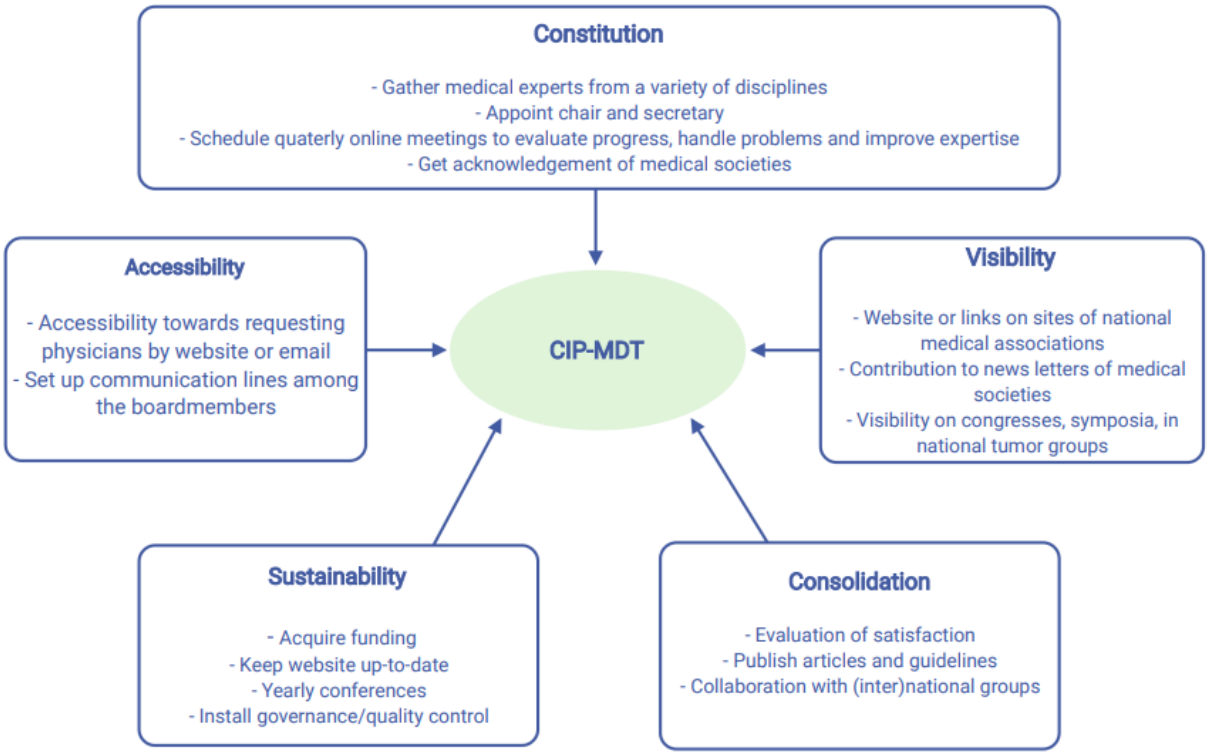


Figure 4. Flowchart of the steps taken at the foundation of a CIP-MDT. Figure created with *BioRender.com*

As stated previously, the CIP-MDT offers recommendations on how and if standard treatment is possible during pregnancy. A presentation of pros and cons as discussed by the CIP-MDT can be outlined in the recommendations to support a shared decision between health care professional and patient.

It should always be taken into account that the requesting physician has the most insight in their patient's preferences, characteristics and social situation, and remains responsible for the initiated treatment plan.

Our study shows that logistic difficulties and geographical barriers for expertise needed can be overcome by a virtual CIP-MDT. Based on the results of this CIP-MDT, an overarching international CIP-MDT has been launched this year (www.ab-cip.org) and facilitates establishment of several national CIP-MDTs. Although platforms to collect data and answer research questions regarding cancer and pregnancy, like the International Network on Cancer, Infertility and Pregnancy (INCIP), already exist, the CIP-MDT has the potential to improve clinical care for these patients as it draws on the expertise and information gained from registering pregnant patients with cancer in higher numbers than any single institution can incrual.[35]

This study gives retrospective insight in the working methods of a national CIP-MDT. Almost 10 years of experience and increasing numbers of requests show that this initiative is highly appreciated and addresses a clinical need. Limitations of this study are the observational and retrospective character, taking into consideration that prospective or randomized studies are barely possible in this field. Outcomes and patient satisfaction were not documented. Therefore, the impact our CIP-MDT had on the treatment plan and outcome of patients could not be described. Future documentation of the advice next to inclusion of these patients in (inter)national registries, will give insight whether CIP-MDTs improves clinical outcome of patients.[35]

REFERENCES

1 Han SN, Kesic VI, Van Calsteren K, et al. Cancer in pregnancy: a survey of current clinical practice. *Eur J Obstet Gynecol Reprod Biol* 167(1):18-23 (2013).
2 de Haan J, Verheecke M, Van Calsteren K, et al. Oncological management and obstetric and neonatal outcomes for women diagnosed with cancer during pregnancy: a 20-year international cohort study of 1170 patients. *The Lancet Oncology* 19(3):337-46 (2018).
3 Thenappan A, Halaweish I, Mody RJ, et al. Review at a multidisciplinary tumour board impacts critical management decisions of pediatric patients with cancer. *Pediatric Blood & Cancer* 64 (2):254-58 (2017).
4 La Nasa M, Gaughan J, Cardonick E. Incidence of Neonatal Neutropenia and Leukopenia After In Utero Exposure to Chemotherapy for Maternal Cancer. *American Journal of Clinical Oncology* 42(4):351-54 (2019).
5 Cardonick E, Iacobucci A. Use of chemotherapy during human pregnancy. *The Lancet Oncology* 5(5):283-91 (2004).
6 Peccatori FA, Azim HA, Jr., Orecchia R, et al. Cancer, pregnancy and fertility: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 24 Suppl 6:vi160-70 (2013).
7 Bézu C, Coutant C, Salengro A, et al. Anaphylactic response to blue dye during sentinel lymph node biopsy. *Surgical Oncology* 20(1):e55-e59 (2011).
8 Amant F, Berveiller P, Boere IA, et al. Gynecologic cancers in pregnancy: Guidelines based on a third international consensus meeting. *Annals of Oncology* 30(10):1601-12 (2019).

9 Van den Broek NR, Lopes AD, Ansink A, et al. "Microinvasive" adenocarcinoma of the cervix implanting in an episiotomy scar. *Gynecol Oncol* 59(2):297-9 (1995).
10 Baloglu A, Uysal D, Aslan N, et al. Advanced stage of cervical carcinoma undiagnosed during antenatal period in term pregnancy and concomitant metastasis on episiotomy scar during delivery: a case report and review of the literature. *Int J Gynecol Cancer* 17(5):1155-9 (2007).
11 Arakawa A, Ichikawa H, Kubo T, et al. Vaginal Transmission of Cancer from Mothers with Cervical Cancer to Infants. *N Engl J Med* 384(1):42-50 (2021).
12 Bhatla N, Aoki D, Sharma DN, et al. Cancer of the cervix uteri. *International Journal of Gynecology and Obstetrics* 143:22-36 (2018).
13 Santolaria A, Perales A, Montesinos P, et al. Acute Promyelocytic Leukemia during Pregnancy: A Systematic Review of the Literature. *Cancers (Basel)* 12(4) (2020).
14 Maggen C, Dierickx D, Lugtenburg P, et al. Obstetric and maternal outcomes in patients diagnosed with Hodgkin lymphoma during pregnancy: a multicentre, retrospective, cohort study. *The Lancet Haematology* 6(11):e551-e61 (2019).
15 Lishner M, Avivi I, Apperley JF, et al. Hematologic malignancies in pregnancy: Management guidelines from an international consensus meeting. *Journal of Clinical Oncology* 34(5):501-08 (2016).
16 Palani R, Milojkovic D, Apperley JF. Managing pregnancy in chronic myeloid leukaemia. *Ann Hematol* 94 Suppl 2:S167-76 (2015).
17 Borgers JSW, Heimovaara JH, Cardonick E, et al. Immunotherapy for cancer treatment during pregnancy. *The Lancet Oncology* 22(12):e550-e61 (2021).
18 Pavlidis N, Pentheroudakis G. Metastatic involvement of placenta and foetus in pregnant women with cancer. *Recent Results Cancer Res* 178:183-94 (2008).
19 Vandecaveye V, Amant F, Lecouvet F, et al. Imaging modalities in pregnant cancer patients. *International journal of gynecological cancer : official journal of the International Gynecological Cancer Society* 31(3):423-31 (2021).
20 Gatta G, van der Zwan JM, Casali PG, et al. Rare cancers are not so rare: the rare cancer burden in Europe. *Eur J Cancer* 47(17):2493-511 (2011).
21 Verheecke M, Halaska MJ, Lok CA, et al. Primary brain tumours, meningiomas and brain metastases in pregnancy: report on 27 cases and review of literature. *Eur J Cancer* 50(8):1462-71 (2014).
22 McGrane J, Bedford T, Kelly S. Successful pregnancy and delivery after concomitant temozolomide and radiotherapy treatment of glioblastoma multiforme. *Clin Oncol (R Coll Radiol)* 24(4):311 (2012).
23 Evans AC, Nelson MB, Dhall G. Pregnancy in a Patient With a Malignant Brain Tumour Taking Temozolomide: Case Report and Review of the Literature. *J Pediatr Oncol Nurs* 32(5):326-8 (2015).
24 Vandenbroucke T, Han SN, Van Calsteren K, et al. Psychological distress and cognitive coping in pregnant women diagnosed with cancer and their partners. *Psycho-Oncology* (2017)
25 Smith LH, Danielsen B, Allen ME, et al. Cancer associated with obstetric delivery: results of linkage with the California cancer registry. *Am J Obstet Gynecol* 189(4):1128-35 (2003).
26 Lee YY, Roberts CL, Dobbins T, et al. Incidence and outcomes of pregnancy-associated cancer in Australia, 1994-2008: a population-based linkage study. *BJOG* 119(13):1572-82 (2012).
27 Parazzini F, Franchi M, Tavani A, et al. Frequency of Pregnancy Related Cancer: A Population Based Linkage Study in Lombardy, Italy. *International journal of gynecological cancer : official journal of the International Gynecological Cancer Society* 27(3):613-19 (2017).
28 Netherlands. CBoSot. Bevolking en bevolkingsontwikkeling per maand; 1995-2018. https://opendata.cbs.nl/statline/#/CBS/nl/dataset/37943ned/table [accessed 27-01 2021]
29 de Haan J, Verheecke M, Van Calsteren K, et al. Oncological management and obstetric and neonatal outcomes for women diagnosed with cancer during pregnancy: a 20-year international cohort study of 1170 patients. *The Lancet Oncology* 19(3):337-46 (2018).
30 Commission E. Conference Report. 3rd Conference on European Reference Networks; 2017 March 9-10 https://ec.europa.eu/health/sites/health/files/ern/docs/ev_20170309_frep_en.pdf2017 [accessed 27-01 2021].
31 Organization WH. Priority diseases and reasons for inclusion - Rare diseases https://www.who.int/medicines/areas/priority_medicines/Ch6_19Rare.pdf [accessed 27-01 2021].
32 Lok C, Amant F. Editorial: The challenge of treating and investigating rare gynaecologic cancers. *Curr Opin Oncol* 33(5):432-34 (2021)
33 Blay JY, Coindre JM, Ducimetière F, et al. The value of research collaborations and consortia in rare cancers. *Lancet Oncol* 17(2):e62-e69 (2016).

34 Ray-Coquard I, Pujade Lauraine E, Le Cesne A, et al. Improving treatment results with reference centres for rare cancers: where do we stand? *Eur J Cancer* 77:90-98 (2017).
35 Maggen C, Wolters V, Cardonick E, et al. Pregnancy and Cancer: the INCIP Project. *Curr Oncol Rep* 22(2):17 (2020).

Chapter 6 The Advisory Board on Cancer, Infertility and Pregnancy: a virtual on-demand multidisciplinary tumour board

Frédéric Amant, **Joosje Heimovaara**, Kristel Van Calsteren, Christianne Lok

The Lancet Oncology, December 2022

Multidisciplinary consultations are part of standard oncological care. These consultations ensure that patients' cases are discussed by all involved specialists and that a consensus is reached on the most appropriate treatment course.[1] The multidisciplinary consultation model is adequate for most patients with cancer, but teams might have insufficient expertise for people with rare cancers or conditions. Cancer during pregnancy is an example of such a rare condition, for which the traditional single-centre multidisciplinary team might not have the expertise to provide a recommendation. Annually in Europe, only 2000–4000 pregnant women are diagnosed with cancer.[2] Although this number might slowly increase because of increasing maternal age and non-invasive prenatal testing, the incidence is expected to stay low and individual expertise will be difficult to develop.

Substantial evidence exists that cancer staging and treatment are possible during pregnancy under some conditions[3,4], but many physicians treating these patients have insufficient knowledge of the detailed information on treatment and outcome that is available. Complexity is further fuelled by the continuous development of new treatment methods that are used earlier and earlier in the course of cancer treatment. As part of the success of these methods, questions have emerged regarding the safety of targeted therapies and immunotherapies during pregnancy.[5] Moreover, ethical issues arise for some individual patients when there is no optimal treatment plan for both mother and fetus during pregnancy or when an optimal treatment for one would be the opposite of the optimal treatment for the other.

Based on this complexity and scarcity of individual experience, experts in the field are frequently consulted by mail or phone for advice on individual patients. However, because of the varied cancer types occurring at different gestational ages, it is very likely that even this individual expertise cannot sufficiently deal with all situations. Additionally, although available consensus papers are helpful and provide general indications, they do not give specific advice at an individual level.[6-8]

The realisation of potentially inadequate advice at the single expert level motivated us to explore the feasibility of a multidisciplinary team for patients who are pregnant and have cancer. However, a multidisciplinary team for patients who are pregnant and have cancer in every hospital providing oncolog-

ical care might still need to deal with the challenges of low incidence and insufficient expertise. Furthermore, geographical and logistical barriers can hinder referral of patients to hospitals with these dedicated multidisciplinary teams. Alternative ways to provide the most optimal multidisciplinary care to patients who are pregnant and have cancer are therefore highly relevant.

These issues led us to the idea for an Advisory Board on Cancer, Infertility and Pregnancy (ABCIP), working under the umbrella of the International Network on Cancer, Infertility and Pregnancy. Our experience with the Dutch national email-based advisory board (ie, Adviesgroep Kanker en Zwangerschap[9], and knowledge of the Serbian advisory board (ie, Tumor Board for Cancer and Human Reproduction) and the mail-based national advisory board in France (ie, Cancer Associé à La Grossesse) showed the potential of this plan but also the need for an improved functional model that is readily available to all physicians. Thanks to a proof-of-concept grant from the European Research Council and a grant from the Kom op tegen Kanker Foundation (Belgium), we were able to create an online platform for the ABCIP. The ABCIP is a collaboration of different national and regional advisory boards that work independently and discuss incoming advice requests from their region or country within their own board. An overarching international board handles patients with challenging disease or circumstances who need additional expertise and discusses patients from countries without a national or regional board. Physicians who wish to seek recommendations can submit their request and anonymous patient information free of charge and on the website, without a login or password. ABCIP boards are structured so that various medical specialists, including medical oncologists, gynaecological oncologists, maternal–fetal medicine specialists, paediatricians, surgical oncologists, haematologists, radiation oncologists, anaesthesiologists, clinical pharmacologists, medical physicists, and ethical advisors, are involved. All experts can discuss the incoming submissions at any time on a secured forum. The clinical case; potential fetotoxic exposure (eg, radiation exposure, use of radioactive molecules, systemic cytotoxic or modulating treatment, or pelvic surgery); effect of the pregnancy on the maternal outcome; and effect of the maternal disease, oncological treatment, and risk of maternal death on the obstetric and paediatric outcome of the child are carefully discussed within the advisory board. All input is merged in a formal personalised recommendation letter to the requesting physician. ABCIP aims to send back their recommendation within 4–7 days. Since its launch in May, 2021, ABCIP has given advice for more than 100 patients from more than 22 countries. Most discussions were regarding patients with breast cancer (n=35), haematological malignancies (n=18), cervical cancer (n=9), ovarian cancer (n=7), and sarcoma (n=5). Next to an international ABCIP, a Belgian, Danish, Dutch, Polish, and a Spanish–Ibero-American group also operate online. Here, we invite more countries and regions to join ABCIP.

Operating for 17 months, ABCIP appears to be a valuable tool for providing easily accessible, fast, and free-of-charge multidisciplinary advice, without boundaries of hospitals or countries. We believe this

model could not only be valuable for young women with cancer but also for other groups, including patients with rare cancers, rare non-cancer conditions, and complex medical conditions.

REFERENCES

1 Thenappan, A. *et al.* Review at a multidisciplinary tumor board impacts critical management decisions of pediatric patients with cancer. *Pediatric Blood & Cancer* **64 (2)**, 254-258 (2017).

2 Han, S. N., Kesic, V. I., Van Calsteren, K., Petkovic, S. & Amant, Frédéric. Cancer in pregnancy: A survey of current clinical practice. *European Journal of Obstetrics and Gynecology and Reproductive Biology* **167**, 18-23 (2013).

3 Amant, F. *et al.* Pediatric Outcome after Maternal Cancer Diagnosed during Pregnancy. *N Engl J Med* **373**, 1824-1834 (2015).

4 de Haan, J. *et al.* Oncological management and obstetric and neonatal outcomes for women diagnosed with cancer during pregnancy: a 20-year international cohort study of 1170 patients. *The Lancet Oncology* **19**, 337-346 (2018).

5 Borgers, J. S. W. *et al.* Immunotherapy for cancer treatment during pregnancy. *The Lancet. Oncology* **22**, e550-e561 (2021).

6 Amant, F. *et al.* Gynecologic cancers in pregnancy: Guidelines based on a third international consensus meeting. *Annals of Oncology* **30**, 1601-1612 (2019).

7 Lishner, M. *et al.* Hematologic malignancies in pregnancy: Management guidelines from an international consensus meeting. *Journal of Clinical Oncology* **34**, 501-508 (2016).

8 Loibl, S. *et al.* Breast Cancer Diagnosed During Pregnancy: Adapting Recent Advances in Breast Cancer Care for Pregnant Patients. *JAMA Oncol* **1**, 1145-1153 (2015).

9 Heimovaara, J. H. *et al.* Ten-year experience of a national multidisciplinary tumour board for cancer and pregnancy in the Netherlands. *Eur J Cancer* **171**, 13-21 (2022).

Part III Clinical challenges in the field of Cancer in Pregnancy

Chapter 7 Maternal death by cancer in pregnancy: A descriptive study of the International Network on Cancer, Infertility and Pregnancy

Joosje Heimovaara, Evangeline Huis in 't Veld, Christianne Lok, Alvaro Cabrera Garcia, Michael Halaska, Ingrid Boere, Mina Mhallem Gziri, Robert Fruscio, Rebecca Painter, Elyce Cardonick, Marry van den Heuvel-Eibrink, Bianca Masturzo, Kristel Van Calsteren, Lia van Zuylen*, Frédéric Amant*

BJOG: An International Journal on Obstetrics and Gynaecology, 2024
* Contributed equally to this manuscript

ABSTRACT

Objectives To characterize pregnant women diagnosed with primary or recurrent cancer who died during pregnancy, during delivery or within one year postpartum.

Design A descriptive study.

Setting The registry of the International Network on Cancer, Infertility and Pregnancy (INCIP).

Population Women diagnosed with cancer during pregnancy between 2000 and 2022.

Methods Using the INCIP registry database, we compared the characteristics of all women with cancer who died during pregnancy, delivery or within 1 year postpartum with those of all women with cancer who survived the first year postpartum.

Main Outcome Measures Maternal and tumour characteristics and obstetrical and neonatal outcomes.

Results Of the 2359 women registered in INCIP, there were 131 cases (5.6%) of maternal mortality. Lung cancer (64.3% of all registered women with lung cancer; 9/14), gastro-oesophageal cancer (61.9%; 13/21) and acute leukaemia (16.2%; 17/105) had the highest rates of maternal mortality. Maternal mortality was associated with fewer live births compared with the control group without maternal mortality (75.6%; 99/131 vs 90.0%; 1952/2163, p<0.001), more elective caesarean sections (60.4%; 64/104 vs41.2%; 756/1836), p<0.001) and a lower gestational age at (induced) delivery (34.0 vs 37.1 weeks, p<0.001) resulting in more preterm births.

Conclusion Maternal mortality occurred in 5.6% of cancer in pregnancy cases and is associated with adverse perinatal outcomes.

INTRODUCTION

Two decades of dedicated research in the field of cancer during pregnancy have increased awareness of the possibility of cancer treatment during pregnancy. [1,2] This has led to an increased number of women being treated during pregnancy, resulting in more live births and fewer iatrogenic preterm deliveries or terminations of pregnancy. However, the unavoidable reality of maternal death from cancer remains a significant concern. [1]

Maternal mortality refers to all causes of death during pregnancy, within 42 days postpartum, and up to one year postpartum (late maternal death), as defined by the International Classification of Diseases, tenth revision (ICD-10). [3,4] This includes both direct causes related to obstetrical complications and indirect causes related to underlying diseases and treatment. In high-income countries, the maternal mortality ratio ranges from 3 to 11 per 100 000 live births. In recent decades, there has been an increase in the proportion of indirect causes of maternal death, primarily due to psychiatric problems, cardiovascular diseases and COVID-19 related morbidity. [5-7] The most recent 'Mothers and Babies: Reducing Risk through Audits and Confidential Enquiries across the United Kingdom' (MBRRACE-UK) report on maternal mortality in the UK states that the incidence of indirect maternal death owing to malignancies diagnosed during or before pregnancy, ranged over time between 0.1 and 0.5 per 100 000 maternities from 2000 to 2020. [7]

Apart from one study[8], maternal death or palliative treatment during pregnancy is only briefly described as part of a whole cohort study or as a specific subanalysis. [1,9] Curative treatment options during pregnancy dominate the literature for this population and literature mostly focuses on the positive outcomes for the children exposed to cancer therapy in utero. [10,11] Several articles about cancer types frequently diagnosed during pregnancy comparing pregnant cancer patients with non-pregnant controls, have not shown any effect of the pregnancy on the cancer survival of these women, and congenital malformation rates of the new-borns appear similar. [12-15] It is expected that the number of cancer diagnoses during pregnancy will increase. [16] With this increase in diagnoses and awareness, more information is desired on the characteristics of women who may not survive the first year postpartum. The aim of this descriptive study was to gain further insight into the characteristics and obstetrical outcomes of women who died because of pregnancy-related cancer. Additionally, we aimed to describe the timing of the oncological diagnosis, delivery, and intent of treatment during pregnancy.

METHODS

This is a descriptive study involving data from the International Network on Cancer, Infertility and Pregnancy (INCIP) (https://www.cancerinpregnancy.org/). The INCIP registry contains data for pregnant

women with a cancer diagnosis and/or -treatment and was approved by the ethical committee of the University Hospital Leuven (B322201421061) and by the national and institutional review boards or ethics committees of all participating centres. Currently the registry contains 2 359 women with active cancer during pregnancy, registered in medical centres mostly from the Netherlands (20.8%), Belgium (20.0%), Italy (13.9%), the USA (12.7%), Russia (11.6%), Mexico (5.8%) and the Chez Republic (5.7%). The full list of registrations per country can be found in the appendix 1. This study describes both retrospectively and prospectively collected oncological and obstetric data for women, diagnosed with cancer during pregnancy between 2000 and 2022. Data collection included the stage and characteristics of the cancer, oncological treatment during pregnancy, obstetrical outcomes and the follow-up of the women.

We compared women who died from a primary or recurrent cancer diagnosis during or within 1 year after pregnancy in the INCIP registry to a control group, consisting of women in the INCIP registry with a primary or recurrent cancer diagnosis during pregnancy who did not die within 1 year after delivery. Maternal mortality was defined according to the World Health Organization (WHO) criteria (including women who died during pregnancy or delivery, and late maternal death). Trimesters of pregnancy were defined as first trimester (0-13+6 weeks of gestation), second trimester (14-26+6 weeks of gestation) and third trimester (from 27 weeks of gestation to birth). Data were analysed using SPSS Statistics 27 (IBM, Armonk, NY, USA). Standardized descriptive analyses were used with medians, percentages and ranges (0-10). Subgroups were analysed using a logistic regression, independent-samples t-test, Fisher's exact test and Mann Whitney-U test.

RESULTS

Between 2000 and 2022, of the 2 359 women in the INCIP registry, there were 131 cases of maternal mortality (5.6%, table 1). The maternal mortality rate decreased over time. (Figure 1) When comparing the different time groups, a significant difference was observed, with a higher level of maternal mortality in the group of women that were pregnant before 2005 compared with the women that were pregnant after 2015. Ten women died during pregnancy (7.6%), 30 women died postpartum within 42 days (22.9%) and 91 women died within 1 year after delivery (69.5%). The median maternal age at cancer diagnosis was 32 years (IQR 28-36 years) in the study group compared with 33 years (IQR 29-36 years) in the control group (p = 0.282). The cases of maternal mortality had a higher percentage of women diagnosed with acute leukaemia, gastro-oesophageal cancer, lung cancer, colorectal cancer and brain tumours than the control group.

	MATERNAL MORTALITY	CONTROL GROUP	P VALUE
TOTAL N	131	2228	
AGE AT DIAGNOSIS, YEARS, MEDIAN (IQR; RANGE)	32 (28-36; 16-54)	33 (29-36; 14-50)	0.282
MISSING	*1*	*26*	
TUMOUR TYPE			
BREAST CANCER	23.7% (n=31)	42.7% (n=951)	<0.001
ACUTE LEUKAEMIA	13% (n=17)	3.9% (n=88)	<0.001
GASTRO-OESOPHAGEAL CANCER	9.9% (n=13)	0.4% (n=8)	<0.001
CERVICAL CANCER	8.4% (n=11)	11.2% (n=249)	0.390
MELANOMA	7.6% (n=10)	4.4% (n=97)	0.084
LUNG CANCER	6.9% (n=9)	0.2% (n=5)	<0.001
COLORECTAL CANCER	6.9% (n=9)	2.4% (n=53)	0.006
BRAIN TUMOUR	6.1% (n=8)	1.9% (n=42)	0.005
(NON) HODGKIN LYMPHOMA	4.6% (n=6)	10.9% (n=244)	0.019
SARCOMA	3.8% (n=5)	1.4% (n=32)	0.051
OVARIAN CANCER	3.1% (n=4)	5.7% (n=126)	0.241
OTHER	6.1% (n=8)	14.8% (n=329)	
PRIMARY DIAGNOSIS OR RECURRENCE			
PRIMARY CANCER DIAGNOSIS DURING PREGNANCY	88.5% (n=116)	94.3% (n=2101)	0.013
RECURRENCE DETECTED DURING PREGNANCY	10.7% (n=14)	4.2% (n=93)	0.002
PREGNANCY DISCOVERED DURING CANCER TREATMENT	0.8% (n=1)	1.5% (n=34)	0.719
TRIMESTER OF DIAGNOSIS			
FIRST TRIMESTER	19.4% (n=24)	27.6% (n=563)	0.480
SECOND TRIMESTER	48.4% (n=60)	41.7% (n=849)	0.160
THIRD TRIMESTER	29.8% (n=37)	25.2% (n=514)	0.245
MISSING	*10*	*303*	
STAGE OF DISEASE			
LOCAL OR REGIONAL	38% (n=46)	72.6% (n=1381)	<0.001
METASTATIC	43.8% (n=53)	6.4% (n=121)	<0.001
HEMATOLOGIC DISEASE	18.2% (n=22)	21% (=399)	0.563
MISSING	*10*	*327*	
TREATMENT DURING PREGNANCY			
NO TREATMENT	9.9% (n=13)	8.7% (n=193)	0.632
PLANNED DELIVERY TO INITIATE CANCER TREATMENT	23.7% (n=31)	11.7% (n=263)	<0.001
SURGERY	22.1% (n=29)	35.3% (n=787)	0.002
CHEMOTHERAPY	37.4% (n=49)	43.8% (n=976)	0.174
RADIATION THERAPY	3.1% (n=4)	2.0% (n=44)	0.338
TARGETED THERAPY	1.5% (n=2)	1.2% (n=27)	0.674
OBSTETRICAL COMPLICATIONS	33.3% (n=38)	29.7% (n=456)	0.399
MISSING	*17*	*692*	
PREGNANCY ENDING			
TOTAL N	131	2163	
LIVE BIRTH	75.6% (n=99)	90.2% (n=1952)	<0.001
TERMINATION OF PREGNANCY	12.2% (n=16)	6.8% (n=148)	0.034
MISCARRIAGE	3.8% (n=5)	1.8% (n=38)	0.095
STILL-BIRTH	1.5% (n=2)	0.8% (n=18)	0.318
DIED WITH FETUS IN UTERO	6.9% (n=9)	0	
MODE OF DELIVERY			
TOTAL N	106	1836	
SPONTANEOUS VAGINAL	29.2% (n=31)	48.5% (n=890)	<0.001
ELECTIVE CAESAREAN SECTION	60.4% (n=64)	41.2% (n=756)	<0.001
EMERGENCY CAESAREAN SECTION	9.4% (n=10)	7.2% (n=132)	0.342
ASSISTED BIRTH (VACUUM/FORCEPS)	0.9% (n=1)	3.2% (n=58)	0.373
LIVEBIRTHS WITH KNOWN GA AT DELIVERY			
TOTAL N	93	1778	
GA AT DELIVERY IN WEEKS (MEDIAN; IQR)	34.0 (31.7-36.6)	37.1 (35.3-38.7)	<0.001
ALL PRETERM DELIVERY	78.5% (n=73)	44.2% (n=785)	<0.001
PLANNED PRETERM DELIVERY	67.7% (n=63)	35.0% (n=623)	<0.001
NEONATES ADMITTED TO THE NICU	70.5% (n=62)	33.1% (n=520)	<0.001

Table 1. Oncological and obstetrical characteristics and neonatal outcomes of patients in the INCIP registry who died of maternal mortality and a control group. *Other tumour types in the maternal mortality group regarded: Two cases of gall bladder cancer, one liver cancer, one pancreatic cancer, one gestational trophoblastic neoplasm, one thyroid cancer, one endometrial cancer and one neuroblastoma. GA: gestational age. NICU: Neonatal intensive care unit.*

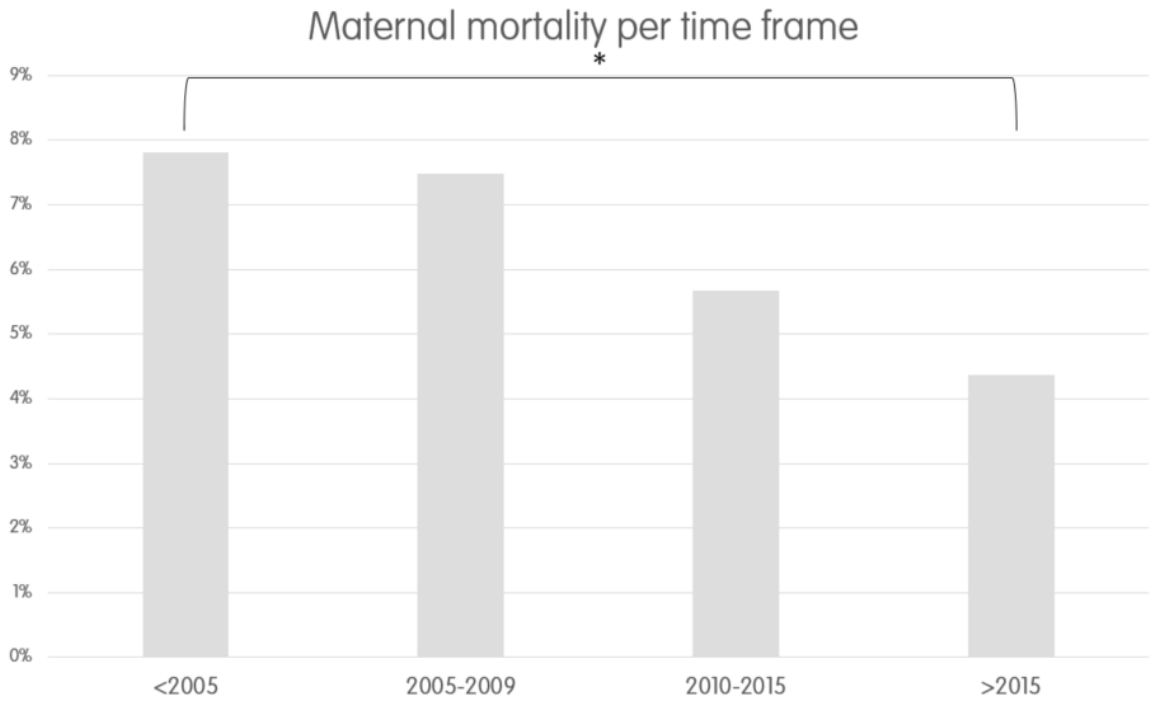


Figure 1 Percentage maternal mortality across time in the International Network on Cancer, Infertility and Pregnancy (INCIP) cohort. **Significance p<0.05.*

Figure 2 shows the total percentage of maternal mortality per cancer type within the INCIP. Of all women in the INCIP registered with lung cancer, 64.3% died within one year after delivery (9/14). Of all women with oesophageal or gastric tumours 61.9% (13/21) died within 1 year after delivery.

The ten women who died during pregnancy are described in detail in table 2. The median maternal age at diagnosis was 35.5 years (range 22-40 years). The median time between diagnosis and death was 6 weeks (IQR 0 – 21.3 weeks). Four women had stage IV disease at presentation. Two women died of sudden death and three died from, or shortly after treatment for their malignancy during pregnancy. Nine women died with their child in utero, at a gestational age of 18.0 and 33.3 weeks, including five with a viable gestational age of more than 24 weeks. The only live birth in this group of ten women was a delivery by a perimortem caesarean section at 36.6 weeks of gestation.

PARITY	TUMOUR	STAGE/GRADE AT DIAGNOSIS/ RECURRENCE DURING PREGNANCY	GA AT DIAGNOSIS/ RECURRENCE	TREATMENT DURING PREGNANCY	OBSTETRICAL OUTCOME	TIME DIAGNOSIS/RECURRENCE - DEATH	CAUSE OF DEATH
G1P0	Melanoma	IV	26+4	Excision melanoma (26+4)	Patient died with fetus in utero (29+0)	2,5 weeks	Sudden death
G4P3	Brain tumour	Glioblastoma multiforme, IV	15+0	Incomplete debulking surgery (18+0)	Patient died with fetus in utero (18+0)	2 weeks	Unknown
G3P1	Gastric cancer	Gastric cancer, M+	15+6	Omentectomy, lymph node biopsy and bilateral oophorectomy (20+4)	Patient died with fetus in utero (21+5)	6 weeks	Unknown
G1P0	Oesophageal carcinoma	Unknown	21+5	Tumor resection (22+0)	Patient died with fetus in utero (30+6)	15,5 weeks	Unknown
G2P1	Brain tumour	Cerebellar medulloblastoma, IV	Post-mortem/post-partum diagnosis	NA	Patient died with 2 fetuses in utero (33+2)	0	Sudden death, tumour identified at autopsy
G14P10	Brain tumour	Glioblastoma multiforme, IV	22+0	Dexamethasone (21+6), prednisone (24+1), open tumour biopsy (28+1) and decompression surgery (32+3)	Patient died with fetus in utero (32+3)	10,5 weeks	Unknown
G8P3	Breast cancer	IV	33+2	Lumpectomy (26+0)	Patient died with fetus in utero (31+0)	20 weeks	Unknown
G2P1	Breast cancer	IIB	11+0	Lumpectomy and sentinel node (14+5), followed by adjuvant 4 cycles AC (17+5) and 8 cycles paclitaxel (28+5)	Child was born at AD 36+4 by emergency peri-mortem caesarean section. Reanimation of the child after birth (APGAR 0-0-2)	25,5 weeks	Hypovolemic shock and ventricular fibrillation
G2P0	Acute myeloid leukemia	Non favourable risk classification	22+1	Cytarabine (22+2)	Patient died with child in utero (22+2)	1 day	Maternal infection on day of diagnosis, severe neutropenia, severe thrombocytopenia, anaemia, leucocytosis, metabolic acidosis/shock
G2P1	Acute lymphatic leukemia	Recurrence	19 weeks before pregnancy	6-mercaptopurine and prednisone	Patient died with fetus in utero (22+0)	41 weeks	Septic shock with multiple organic failure (cardiac, renal, respiratory and haematological).

Table 2. Case descriptions of 10 women that died during pregnancy. *G = gravity, P = parity, NA = not applicable*

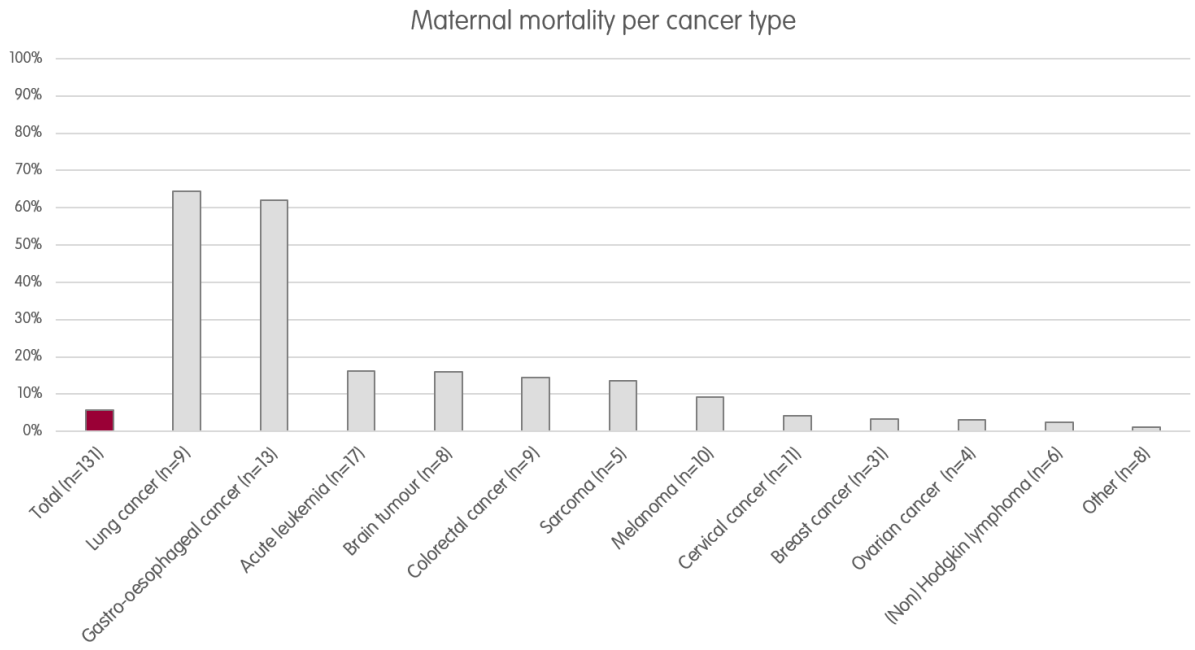


Figure 2 Percentage of maternal mortality by cancer type within the International Network on Cancer, Infertility and Pregnancy (INCIP) cohort.

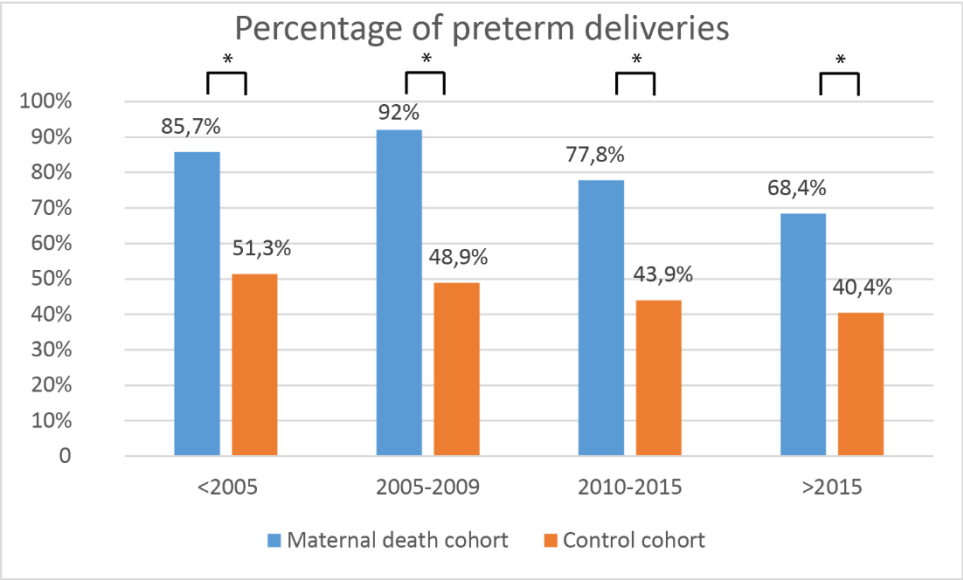
Of the 121 women who died postpartum, 109 died from their cancer. The main causes of mortality were not further specified (n=79), but 16 women died with liver- or brain metastases or bone marrow infiltration noted as underlying cause and eight women died of septic shock unrelated to cancer treatment. In eight women, death was caused by an adverse event of cancer therapy, mostly sepsis and respiratory failure. One woman died of fulminant hepatitis with generalized seizures following the start of Asparaginase therapy. Of the last four women that died postpartum, one died of suicide and the cause of death was not registered for the other three.

Information on treatment plans during pregnancy was available in 102 cases of maternal mortality with solid tumours. Treatment with palliative intent was more common than treatment with curative intent (n=60 (59%) vs 42 (41%), respectively, P<0.001). Significantly more deceased women in our study group initially treated with curative intent had breast cancer, compared with the women in our study group treated with palliative intent (50.0% (n=21) vs 15.0% (n=9), P<0.001). Among the women who died of a haematological malignancy, there were no women who immediately started on treatment with palliative intent.

Obstetrical complications were registered in 114 women and of all these, 33.3% (n=38) of the women had experienced complications during pregnancy (table 1). This did not differ significantly between groups. No differences in numbers of complications were observed between the different tumour types. Of these 38 pregnancies 15 (39%) were complicated by intra-uterine growth restriction, eight

(21%) by gestational diabetes, eight by (maternal) infection during pregnancy (21%), four (11%) were complicated by pre-eclampsia and four (11%) by preterm pre-labour rupture of membranes.

The percentage of live births in all cases of maternal mortality was significantly lower than the percentage of live births in the control group (75.6% and 90.2%, respectively P<0.001, table 1). A higher percentage of women delivered by elective caesarean section compared to the control group (60.4% and 42.2%, respectively, P<0.001). The median gestational age at delivery of all live births in the study group was 34.0 weeks (IQR 31.7-36.6 weeks) compared with 37.1 weeks in the control group (IQR 35.3-38.7 weeks, U = 42839, p<0.001). Significantly more cases of maternal mortality had an induced preterm delivery compared with the control group (67.7% and 35.0%, respectively P<0.001) and significantly more neonates were admitted to the neonatal intensive care unit (NICU) (70.5% vs 33.1%, P<0.001), mostly for prematurity. When looking at the percentage of preterm (induced) deliveries over time (figure 3), both groups showed a decrease of preterm (induced) deliveries over time, although between group differences remained.



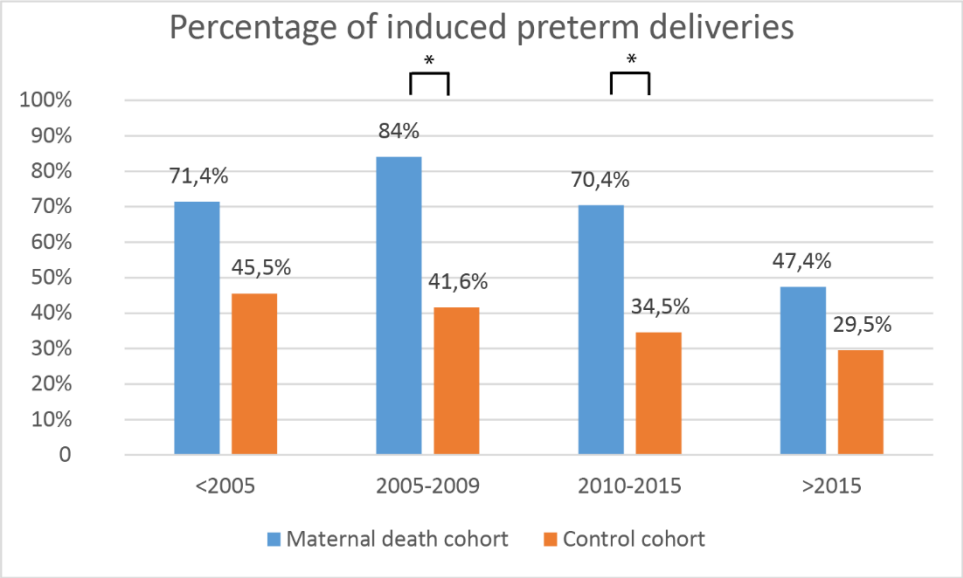


Figure 3. Percentage of (induced) preterm deliveries across time within the International Network on Cancer, Infertility and Pregnancy (INCIP) cohort. **P<0.05.*

DISCUSSION

Main findings

Our study of maternal mortality due to cancer diagnosed during pregnancy shows that, compared with pregnant women with cancer who survived the first year postpartum, lung cancer and gastro-oesophageal tumours are over-represented. In comparison, breast cancer is under-represented, reflecting the generally better oncological outcome for breast cancer within the first year postpartum. Maternal mortality was associated with preterm (induced) delivery, likely echoing concern for the deteriorating

of the maternal condition or necessity for intensive treatment modalities not compatible with pregnancy. Consequently, pregnancies ended mostly with elective caesarean sections and preterm planned deliveries.

Interpretation

Our study demonstrates that among women diagnosed with cancer in pregnancy registered in the INCIP registry, maternal mortality occurred in 56 per 1 000 maternities and a previous article by de Haan et al. reported a maternal mortality rate from cancer of 1.23 per 100 000 live births in the Netherlands, both of these results exceed the rates of maternal mortality described in general obstetric populations. [7,8]The decreasing mortality rate over time found in our study corresponds to previous findings, as shown in the MBRACCE UK report from 2018 to 2020, suggesting the improved treatment of cancer during pregnancy over time. [7]

Since our cohort consists of a specific group of women diagnosed during pregnancy, comparisons with mortality rates in general oncological population is difficult, but our results might indicate poorer survival rates. For example, women aged 15-44 years diagnosed with lung cancer in the UK have a 1-year mortality rate of 31.1%, whereas in our database this rate is 64.3%.[17] When looking at women aged 15-44 with breast cancer in the UK, 1-year mortality rate is 1.4%, which is also lower than the mortality rate of 3.2% presented here. The fact that nearly half of maternal mortality cases occur during the initiation of curative treatment, and that half of the deaths among pregnant women were unexpected, may reflect the general poorer outcomes for certain types of cancer. But no information on tumour stage at diagnosis is taken into consideration when comparing these numbers. Possible explanations for these differences might be a delay in diagnosis, for example owing to pregnancy-mimicking symptoms and delaying imaging, as well as a delay in treatment because of the concurrent pregnancy.
Most women who suffered maternal mortality were diagnosed with a cancer with poor prognosis. It is known that a poor performance status is a prognostic factor for worse outcomes in patients with advanced cancer. A poor performance status puts women at risk of rapid health deterioration during pregnancy. This is reflected in our group, where this risk of rapid deterioration is further emphasized by the increased number of induced preterm births and adverse perinatal outcomes seen in our study group.

Although the number of preterm deliveries decreased over time, probably reflecting the better management of cancer in pregnancy and increases in knowledge, the vast majority of pregnancies of our cases of maternal mortality ended in a preterm delivery, with a median gestational age at delivery of

34 weeks. Most neonates were admitted to the NICU, mainly for prematurity. Two thirds of all deliveries in our cases of maternal mortality were planned preterm, compared with one third in the control group. Prematurity is well known to be the cause of a wide variety of neonatal complications such as intraventricular haemorrhage, bradycardia, respiratory failure, necrotizing enterocolitis, sepsis, seizures, jaundice and hypoglycaemia. A study by Fischer et al. showed that the adverse events seen in preterm born neonates exposed to cancer in utero is mostly related to preterm delivery and not to cancer (treatment) during pregnancy, as the effects of preterm delivery did not differ between neonates born to mothers with cancer during pregnancy and a comparable group of preterm born neonates from healthy mothers. [18] A previous study by Van Assche et al. described the outcomes of 9-year old children born to women with cancer during pregnancy. [11] They concluded that both preterm delivery and maternal death were risk factors for developmental problems in these children, but multilinear analyses showed a correlation between the two, with only gestational age at birth being independently related to developmental problems. Although a poor performance status might have contributed to the decision to accept preterm deliveries in our group, it remains important to take adverse outcomes in the neonates into consideration in this specific group of patients.

Follow-up studies of children born from pregnancies complicated by maternal cancer show overall reassuring neurocognitive outcomes. [10,19,20] However, the long-term outcomes of this specific subset of children are not yet available. A recent study by Egberts et al. looking at children confronted with parental cancer, reported increased trauma-related cognition and difficulties with emotion regulation in general. [21] An article by Cardonick et al. investigating the development of children born after pregnancies with maternal cancer, showed increasing levels of behaviour problems in children evaluated at a later age, suggesting a link with a possible better understanding of their mother's medical condition at an older age. [22] In women with certain cancer types and/or metastatic disease and a poor performance status at diagnosis, the risk of maternal death should be anticipated and appropriate counselling and psychological support should be organized for these families and children. In clinical practice, there is increasing interest in psychosocial support for the mother and her family members but the specific needs of women with cancer during pregnancy and their offspring remain unknown. Despite generally reassuring outcomes of both mother and child after dealing with cancer during pregnancy, continuing psychosocial guidance and monitoring of the family remains indispensable, especially for this subgroup of women with poor prognosis. A more specific elucidation of risks could help provide a structured framework for counselling these patients on family planning – when diagnosed pre-pregnancy, as well as guiding them during pregnancy and facilitating optimal management during the delivery process. The children of these mothers may need long term psychosocial support dedicated to enhancing their quality of life, in addition to routine consultations.

This study clearly shows that cancer in pregnancy is a potentially lethal disease in which concessions should not be accepted lightly, and preferably adjustments to therapy are only made after discussion in a multidisciplinary board. For example, specifically for women with advanced stages of disease and a poor performance status, it could even be important to discuss the possibility of a termination of pregnancy in early pregnancy. As each case is unique and comes with its own difficulties and as the standard treatment cannot always be provided (owing to gestational age or teratogenicity), our maternal death group underpins the need for multidisciplinary consultation. Initiatives like the Advisory Board on Cancer, Infertility and Pregnancy (www.ab-cip.org) may support physicians who need recommendations for pregnant or postpartum women in difficult situations. [23] In addition, physicians should be encouraged to register all cases, including the difficult cases where death is inevitable, to expand on the limited series currently available.

Strengths and limitations

Owing to the observational nature of this= study, no conclusions can be drawn on the population-wide incidence of maternal death. However, the mortality rate in women with the types of cancer found in our study is similar to that in non-pregnant women of fertile age. [24] Moreover, results from large cohort studies using national patient registry data on pregnant cancer patients align with our findings that patients with cancer are at increased risk of mortality at delivery. [25,26] This study aimed to expand knowledge about the consequences of being diagnosed with cancer during pregnancy, by describing the mortality in pregnant cancer patients. As registration in the INCIP is voluntary and partially retrospective, missing data are inevitable. For instance, there may be an underrepresentation of local cancers with curative surgical treatment only and cases of cancer diagnosed in early pregnancy with immediate termination of pregnancy. Additionally, there may be an underreporting of women with a very poor prognosis, as obtaining consent for inclusion might be considered too burdensome. These limitations could suggest the presence of selection bias and attrition, wherein experienced treatment centres (participating in our study) may be more familiar with treating and managing cancer in pregnancy, leading to lower rates of maternal deaths because of their expertise and resources. Although unlikely, this might lead to an underestimation of maternal death rates from cancer in our study. In addition, the voluntary registration in the INCIP may have also led to an underestimation of the number of pregnancy complications noted in our article. Unfortunately, we lacked information on the performance status of the participants at diagnosis. Lastly, by missing non-pregnant controls, information of pregnancy-related treatment modifications and oncological outcomes is lacking in this article, as well as specific pregnancy-related mortality rate differences. To investigate this, age-, tumour type- and

stage-matched non-pregnant controls would need to be included, which would necessitate a long inclusion period because of the low incidences in this specific population.

CONCLUSION

This study demonstrates that in the INCIP registry, the largest cancer in pregnancy cohort to date, maternal mortality occurs in 5.6% of women diagnosed with cancer in pregnancy. Awareness about the possibility of maternal death from cancer and early identification of women at risk for poor maternal outcome, allows for a fair discussion with the woman and her partner and the initiation of adequate palliative care including psychological support for the family after the maternal death.

References

1 de Haan, J. *et al.* Oncological management and obstetric and neonatal outcomes for women diagnosed with cancer during pregnancy: a 20-year international cohort study of 1170 patients. *The Lancet Oncology* **19**, 337-346 (2018).

2 Wolters, V. *et al.* Management of pregnancy in women with cancer. *International journal of gynecological cancer* **31**, 314-322 (2021).

3 ICD-11 Reference guide, Part 2. Geneva: World Health Organization (2019) *(https://icd.who.int/icd11refguide/en/index.html#2.17.2DataSourceIntlDeathCertificate|data-source-the-international-deathcertificate|c2-17-2 (accessed 20th dec 2022).*

4 Application of ICD-10 to deaths during pregnancy, childbirth and the puerperium: ICD maternal mortality (ICD-MM). Geneva: World Health Organization; (2012) *(https://www.who.int/publications-detail-redirect/9789241548458 (accessed 20 Dec 2022)*.

5 Kassebaum, N. J. *et al.* Global, regional, and national levels and causes of maternal mortality during 1990-2013: a systematic analysis for the Global Burden of Disease Study 2013. *Lancet* **384**, 980-1004 (2014).

6 Diguisto, C. *et al.* Maternal mortality in eight European countries with enhanced surveillance systems: descriptive population based study. *BMJ* **379**, e070621 (2022).

7 Knight M, B. K., Patel R, Shakespeare J, Kotnis R, Kenyon S, Kurinczuk JJ (Eds.) on behalf of MBRRACE-UK. Saving Lives, Improving Mothers' Care Core Report - Lessons learned to inform maternity care from the UK and Ireland Confidential Enquiries into Maternal Deaths and Morbidity 2018-20. *Oxford: National Perinatal Epidemiology Unit, University of Oxford 2022.* (2020).

8 de Haan, J., Lok, C. A. R., Schutte, J. S., van Zuylen, L. & de Groot, C. J. M. Cancer related maternal mortality and delay in diagnosis and treatment: a case series on 26 cases. *BMC pregnancy and childbirth* **18**, 10 (2018).

9 van Gerwen, M. *et al.* Long-term neurodevelopmental outcome after prenatal exposure to maternal hematological malignancies with or without cytotoxic treatment. *Child Neuropsychol* **27**, 822-833 (2021).

10 Vandenbroucke, T. *et al.* Child development at 6 years after maternal cancer diagnosis and treatment during pregnancy. *Submitted* (2020).

11 Van Assche, I. A. *et al.* Cognitive and Behavioral Development of 9-Year-Old Children After Maternal Cancer During Pregnancy: A Prospective Multicenter Cohort Study. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*, Jco2202005 (2023).

12 Maggen, C. *et al.* Obstetric and maternal outcomes in patients diagnosed with Hodgkin lymphoma during pregnancy: a multicentre, retrospective, cohort study. *The Lancet Haematology* **6**, e551-e561 (2019).

13 Halaska, M. J. *et al.* Characteristics of patients with cervical cancer during pregnancy: A multicenter matched cohort study. An initiative from the International Network on Cancer, Infertility and Pregnancy. *International Journal of Gynecological Cancer* **29**, 676-682 (2019).

14 Amant, F. *et al.* Outcome of breast cancer patients treated with chemotherapy during pregnancy compared with non-pregnant controls. *Eur J Cancer* **170**, 54-63 (2022).
15 Houlihan, O. A., Buckley, D., Maher, G. M., McCarthy, F. P. & Khashan, A. S. Maternal and perinatal outcomes following a diagnosis of Hodgkin lymphoma during or prior to pregnancy: A systematic review. *Bjog* **130**, 336-347 (2023).
16 Lenaerts, L., Jatsenko, T., Amant, F. & Robert Vermeesch, J. Noninvasive Prenatal Testing and Detection of Occult Maternal Malignancies. *Clinical chemistry* **65**, 1484-1486 (2019).
17 NHS Digital. Cancer Survival in England, cancers diagnosed 2016 to 2020, followed up to 2021 (2023) https://digital.nhs.uk/data-and-information/publications/statistical/cancer-survival-in-england (accessed 14-5-2024)
18 Fischer, D., Ahr, A., Schaefer, B., Veldman, A. & Schloesser, R. Outcome of preterm and term neonates of mothers with malignant diseases diagnosed during pregnancy. *J Matern Fetal Neonatal Med* **19**, 101-103 (2006).
19 Amant, F. *et al.* Long-term cognitive and cardiac outcomes after prenatal exposure to chemotherapy in children aged 18 months or older: An observational study. *The Lancet Oncology* **13**, 256-264 (2012).
20 Amant, F. *et al.* Pediatric outcome after maternal cancer diagnosed during pregnancy. *New England Journal of Medicine* **373**, 1824-1834 (2015).
21 Egberts, M. R. *et al.* Child Posttraumatic Stress after Parental Cancer: Associations with Individual and Family Factors. *J Pediatr Psychol* **47**, 1031-1043 (2022).
22 Cardonick, E. H., Gringlas, M. B., Hunter, K. & Greenspan, J. Development of children born to mothers with cancer during pregnancy: Comparing in utero chemotherapy-exposed children with nonexposed controls. *American Journal of Obstetrics and Gynecology* (2015).
23 Amant, F., Heimovaara, J. H., Lok, C. A. R. & Van Calsteren, K. The Advisory Board on Cancer, Infertility and Pregnancy: a virtual on-demand multidisciplinary tumour board. *The Lancet Oncology* (2022).
24 Dyba, T. *et al.* The European cancer burden in 2020: Incidence and mortality estimates for 40 countries and 25 major cancers. *Eur J Cancer* **157**, 308-347 (2021).
25 Greiber, I. K. *et al.* Cancer in pregnancy and the risk of adverse pregnancy and neonatal outcomes: A nationwide cohort study. *BJOG* **129**, 1492-1502 (2022).
26 Sundermann, A. C. *et al.* Maternal morbidity and mortality among patients with cancer at time of delivery. *Am J Obstet Gynecol* **229**, 324.e321-324.e327 (2023).

Chapter 8 Obstetric and oncological outcomes of patients diagnosed with sarcoma during pregnancy: A report on cases from the INCIP and review of literature

Joosje Heimovaara, Charlotte LeJeune, Daphne Hompes, Christianne Lok, Isabelle Ray-Coquard, Kristel Van Calsteren, Lia van Zuylen, Katrijn Debyser, Elyce Cardonick, Rebecca Painter, Els Witteveen, Alvaro Cabrera Garcia, Roman Shmakov, Frédéric Amant, for the International Network on Cancer, Infertility and Pregnancy

Submitted

ABSTRACT

Purpose Sarcomas in pregnancy are rare events that require a multidisciplinary approach balancing oncological treatment and maternal-fetal well-being. Lack of knowledge complicates treatment decisions and counselling of patients. This study aims to provide more insight into tumour characteristics, treatment and obstetric outcomes of these patients.

Methods Cases of sarcoma in pregnancy were retrieved from the International Network on Cancer, Infertility, and Pregnancy (INCIP) registry, supplemented by cases identified in a systematic review of literature describing patients with sarcoma during pregnancy.

Results Between January 2000 and August 2023, 162 patients with primary or recurrent sarcoma in pregnancy were included; 45 cases within INCIP and 117 cases retrieved from literature. Soft tissue sarcomas (STS) were the most frequent subtype (77.8%). Median age at primary diagnosis was 29 years (9-44). Metastatic disease was present in 25.6% of the patients. Common symptoms at presentation included a growing mass, pain and dyspnoea. Forty-six patients had an expectative management during pregnancy. Surgery (38.9%) and chemotherapy (17.3%) were the most common treatments during pregnancy. Fifty-five patients underwent induction of labour and 14 first trimester pregnancy terminations.

Known obstetric outcomes of 147 patients were 83% live births, 9.5% terminations and 3.4% stillbirths. 56.3% underwent elective caesarean section. 65.2% of live births were preterm. Median birth weight was 2375 grams (690-4465), and 3.8% of the neonates had congenital malformations.

Of 136 patients with known oncological follow up, median follow-up time was 22 months (0-160); recurrence rate was 43.4%; and maternal death rate 38.2%.

Discussion This study highlights the often poor prognosis in pregnant sarcoma patients and high rates of preterm induced delivery. Sarcoma symptoms might mimic common pregnancy ailments, possibly explaining delayed diagnosis leading to the high percentage of metastatic disease.

INTRODUCTION

Sarcomas account for 1-2% of all adult cancers and represent a group of rare and heterogeneous malignant tumours of mesenchymal origin, divided into soft tissue sarcomas (STS) and non-soft tissue sarcomas (NSTS), with more than 70 subtypes in total. [1,2] Histological subtype and tumour grade constitute the primary determinants of prognosis. [3] Although sarcomas are more common in older patients, STS account for 8% of all malignant tumours in young adults, and osteosarcomas and Ewing sarcomas have a relatively high incidence in the second and third decades of life. [2,4,5] Sarcoma may therefore occur during pregnancy. They represent 5% of all cancers diagnosed during pregnancy. [6,7]

The European Society or Medical Oncology (ESMO) has developed clinical practice guidelines for the treatment of STS and NSTS. f[8,9] Treatment options encompass a range of interventions, including surgery, radiation therapy and chemotherapy. The wide variability in behaviour and molecular characteristics of different sarcoma subtypes makes it challenging and sometimes time consuming to determine the appropriate diagnosis and subsequent therapy for each individual patient. [10,11] It is imperative to adopt a multidisciplinary approach that tailors treatment to the needs of pregnant patients. [12] The challenge lies in the balance between optimal oncological treatment for the mother and the well-being of the child. Treatment should adhere as closely as possible to the standard of care outside pregnancy, in order to not to deteriorate maternal prognosis.

Surgery of extra-uterine sarcomas can often be safely performed during pregnancy – regardless of gestational age – with certain precautions. Radiation therapy, with the exception of abdominal irradiation, can be carried out if the cumulative fetal radiation dose is kept below 100 mSv throughout the pregnancy. [13,14] Careful planning is necessary when treating pregnant patients, including estimating the total fetal exposure based on the radiation dose and the distance of the radiation field from the fetus.

Chemotherapy is associated with an increased risk of congenital malformations when administered during organogenesis in early gestation. [15,16] Furthermore, chemotherapy is known to cross the placenta to some extent, and when administered after the first trimester, intra-uterine growth restriction, preterm contractions and placental insufficiency have been reported. However, follow-up of the children exposed to chemotherapy during the second or third trimester shows reassuring results. [16,17] Therefore, various chemotherapeutic agents can be administered during pregnancy from the second trimester onwards in order to prevent treatment delay, while also avoiding termination of pregnancy (TOP) or medically indicated preterm delivery. Commonly used chemotherapeutic agents in NSTS outside of pregnancy include doxorubicin, cisplatin, high dose methotrexate (MTX), and ifosfamide, while doxorubicin and ifosfamide are the first choice in STS. Doxorubicin crosses the placenta, resulting in umbilical cord concentrations of less than 10% compared to maternal concentrations, and is associated

with small for gestational age (SGA) and premature rupture of membranes. Cisplatin has a transplacental transfer of 2-24% and is associated with SGA and neonatal ototoxicity. [18,19] MTX is teratogenic and reports of aminopterin syndrome have led to an absolute contra-indication for its use in pregnancy. [20] The extent of transplacental ifosfamide transfer is unknown, but an association between administration during pregnancy and oligohydramnios has been described. [21]

Targeted agents, such as imatinib, pazopanib and neurotrophic tyrosine receptor kinase (NTRK) inhibitors, are becoming more common in the routine treatment of sarcomas. Imatinib has been linked with congenital malformations when administered before 12 weeks of gestation. Nonetheless, it is increasingly being used from the second trimester onwards. [22] NTRK inhibitors, such as larotrectinib and entrectinib, have been associated with congenital malformations in animal studies. [23,24] Data concerning the use of these agents in human pregnancy are lacking.

The literature notably lacks large cohort studies or case series on STS or NSTS during pregnancy. This complicates treatment choices and counselling during pregnancy. The aim of this study was to describe a large collection of patients with sarcoma during pregnancy to provide further insights into the tumour characteristics and oncological and obstetrical outcomes of these patients.

METHODS

For this descriptive study, all patients diagnosed with primary or recurrent STS or NSTS during pregnancy diagnosed between January 2000 and August 2023 were selected from the database of the International Network on Cancer, Infertility and Pregnancy registry (INCIP; Clinicaltrials.gov, number NTC00330447). The international registration study was approved by the Ethics Committee of the University Hospitals of Leuven (Belgian number 322201421061) and the participating centres according to local policies. This study describes both retro- and prospectively collected patient data on oncological treatment, obstetrical outcomes and follow-up of patients with any pregnancy-associated malignancy. On the 1st of March 2024, the registry contained 2959 patients with cancer during pregnancy, registered by 79 European and non-European centres in 28 countries.

In addition, a systematic review was conducted searching for case reports and case series of STS and NSTS during pregnancy. Articles were identified by a PUBMED search using the following MESH terms: ‘pregnancy’, ‘sarcoma’ and variations thereof. All specific search criteria can be found in the Supplementary Appendix A. Two reviewers independently screened all potentially relevant titles and abstracts for eligibility. The reviewers also assessed the eligibility of the full-text articles in duplo. Disagreements were resolved by consensus. Articles were included if the design was a case report or case series describing at least one patient with known treatment modalities during pregnancy, who met the inclusion

criteria. We excluded articles published before 2000, written in another language than English, if full text was not available or if individual patient data could not be extracted.

The full text of the selected articles was acquired for further review. We evaluated the methodological quality of the included studies with an assessment tool created for this review specifically, since no validated scoring system for case reports exists until this day. We adjusted the JBI critical appraisal checklist for case reports. [25] Full scoring can be found in Supplementary Appendix B. After gathering all eligible articles, we reviewed tumor types, age at diagnosis and country to ensure there were no double inclusions. Data on tumor characteristics, treatment and obstetric and oncological outcome were extracted.

Trimesters of pregnancy were defined as first trimester (0-13+6 weeks), second trimester (14-26+6 weeks) and third trimester (27 weeks - birth). Types of treatment were analyzed separately, with patients potentially undergoing different types of treatment simultaneously or consecutively. Miscarriage refers to loss of a pregnancy before 22 weeks as defined by, according to the World Health Organization definition, whereas stillbirth refers to the loss of a pregnancy after 22 weeks. Induction of delivery was denoted as an obstetric intervention that stimulates the onset of labor using artificial methods. [26] Preterm delivery was denoted as a delivery before 37 weeks of gestation. Data were analyzed using IBM SPSS Statistics (version 27). Standardized descriptive analyses were used with medians, percentages and interquartile ranges (IQR) rounded to whole numbers, and ranges.

RESULTS

Between January 2000 and August 2023, 162 patients diagnosed with sarcoma during pregnancy were identified, of whom 45 patients were included in the INCIP registry and 117 cases were retrieved from literature. Figure 1 shows a flow chart of the search, selection and case extraction process according to the PRISMA guidelines.

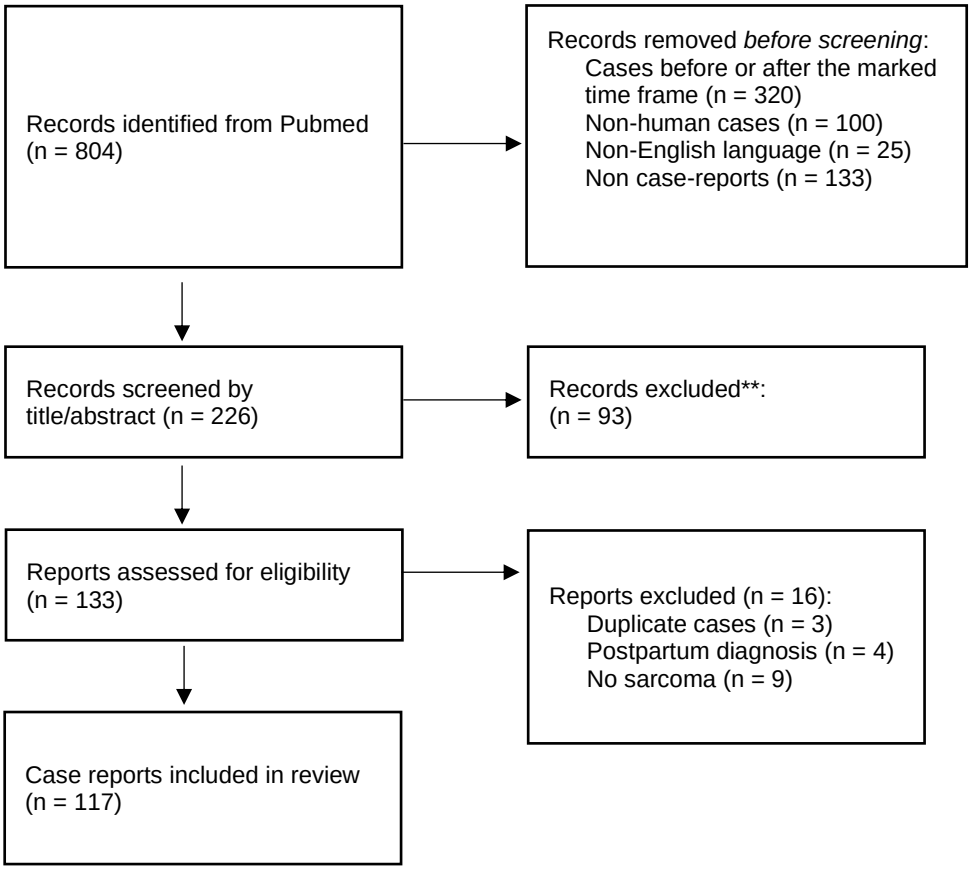


Figure 1. PRISMA (Preferred Reporting Items for Systematic Review and Meta-analysis) flowchart for selected case reports. ***exclusion criteria included: benign lesions (n=7), Postpartum diagnosis (n=14), congenital malignancies (n=40), no pregnancy (n=28), pregnancy after diagnosis and treatment (n=20), No diagnosis of sarcoma (n= 17), animal cases (n=5), no case report (n=1) or a case before 2000 (n=1).*

The median age at primary diagnosis of the whole group was 29 years (range 9-44). Twenty-two patients (13.6%) were diagnosed with a recurrence during pregnancy. The median gestational age at diagnosis was 23 weeks (ranging from becoming pregnant until during treatment to 41 weeks of gestation). STS was diagnosed in 126 patients (77.8%) and NSTS in 36 patients (22.2%). A complete overview of the characteristics of the INCIP cases and the total group can be found in table 1. A complete overview of subtypes is shown in Supplementary Appendix B. Thirty-six patients were diagnosed with metastatic disease (26.5%). Table 2 shows the symptoms at first presentation. Most patients reported a growing mass (33.3%, n=54), pain (30.2%, n=49), oedema (16.0%, n=26), dyspnoea (13.6%, n=22) or vomiting (6.8%, n=11).

	INCIP	LITERATURE	ALL
TOTAL NUMBER OF CASES	45	117	162
AGE AT DIAGNOSIS; YEARS, MEDIAN (IQR; RANGE)	29 (25-35; 15-40)	29 (25-33; 9-44)	29 (25-33; 9-44)
MISSING	7	2	9
GA AT DIAGNOSIS; WEEKS, MEDIAN (IQR; RANGE)	18 (12-29; 0-41)	25 (19-31; 8-39)	23 (16-30; 0-41)
MISSING	0	7	7
TRIMESTER OF DIAGNOSIS; % (N)			
FIRST TRIMESTER	31.1 (14)	9.6 (11)	15.7 (25)
SECOND TRIMESTER	40.0 (18)	46.5 (53)	44.7 (71)
THIRD TRIMESTER	28.9 (13)	43.9 (50)	39.6 (63)
MISSING	0	3	3
TYPE OF SARCOMA; % (N)			
STS	68.9 (31)	81.2 (95)	77.8 (126)
NSTS	31.1 (14)	18.8 (22)	22.2 (36)
RECURRENCE DURING PREGNANCY; % (N)	17.8 (8)	12 (14)	13.6 (22)
DISTANT METASTASES AT DIAGNOSIS; % (N)	30.3 (10)	25.2 (26)	26.5 (36)
MISSING	12	14	26
TREATMENT DURING PREGNANCY; % (N)			
EXPECTATIVE MANAGEMENT	26.7 (12)	29.1 (34)	28.4 (46)
INDUCTION OF LABOR/TOP TO INITIATE CANCER TREATMENT POSTPARTUM	42.2 (19)	42.7 (50)	42.6 (69)
SURGERY	40 (18)	38.5 (45)	38.9 (63)
CHEMOTHERAPY	28.9 (13)	12.8 (15)	17.3 (28)
RADIATION THERAPY	6.7 (3)	3.4 (4)	4.3 (7)
OTHER THERAPY	0	2.6 (3)	1.9 (3)
PREGNANCY ENDING; % (N)			
LIVE BIRTH	77.3 (34)	85.4 (88)	83.0 (122)
TERMINATION OF PREGNANCY	15.9 (7)	6.8 (7)	9.5 (14)
STILL BIRTH	4.5 (2)	2.9 (3)	3.4 (5)
MISCARRIAGE	2.3 (1)	1.9 (2)	2.0 (3)
ONGOING PREGNANCY	0	2.9 (3)	2.0 (3)
MISSING	1	14	15
MODE OF DELIVERY LIVEBIRTHS; % (N)	n = 34	n = 78	n = 112
SPONTANEOUS	20.6 (7)	21.8 (17)	21.4 (24)
INDUCTION OF DELIVERY	41.2 (14)	14.1 (11)	22.3 (25)
ELECTIVE CAESAEREAN SECTION	38.2 (13)	64.1 (50)	56.3 (63)
LIVEBIRTHS	n = 34	n = 78	n = 112
PRETERM DELIVERY; % (N)	55.9 (19)	69.1 (56)	65.2 (75)
GA AT DELIVERY IN WEEKS; MEDIAN (IQR; RANGE)	36 (34-39; 25-42)	35 (32-37; 27-42)	35 (32-37; 25-42)
MISSING	0	2	2
NEONATAL WEIGHT AT BIRTH; MEDIAN (IQR; RANGE)	2510 (1890-3031; 690-4465)	2200 (1712-2948; 850-3990)	2375 (1850-3001; 690-4465)
MISSING	6	28	34
CONGENITAL MALFORMATIONS; % (N)	3.3 (1)	4 (2)	3.8 (3)
MISSING	4	28	32
FOLLOW-UP MOTHER			
RECURRENCE; % (N)	53.1 (17)	39.5 (32)	43.4 (49)
DEATH; % (N)	52.6 (20)	32.7 (32)	38.2 (52)
FU TIME IN MONTHS; MEDIAN (IQR; RANGE)	29 (21-71; 6-160)	13 (6-34.5; 0-120)	22 (10-48; 0-160)
MISSING	7	36	43

Table 1. Patient characteristics**.** Types of treatment were analysed separately, with patients potentially undergoing different types of treatment simultaneously or consecutively. *IQR: interquartile range, GA: gestational age, TOP: termination of pregnancy, PF: progression free survival, OS: overall survival*

Figure 2 shows an overview of the treatment modalities during pregnancy. Figure 2a shows the types of treatment given during pregnancy by trimester. Treatment was not initiated during pregnancy in 28.4% of all pregnant patients with sarcoma (n=46, table 1), primarily patients diagnosed during the third trimester. Surgery was performed during pregnancy in 38.9% (n=63), mostly in the first trimester. The most common surgical sites were extremities (25%, n=14), bowel (21%, n=12), thorax/heart (19%, n=11) or breast (14%, n=8, figure 2b). Chemotherapy was given during pregnancy in 17.3% of the patients (n=28). Most patients had a Ewing sarcoma (n=6), osteosarcoma (n=5) or breast sarcoma of unspecified subtype. Most patients were treated with (a combination of) doxorubicin (29%, n=15), cyclophosphamide (17%, n=9), ifosfamide (11%, n=6), vincristine (10%, n=5) and actinomycin-D (10%, n=5, figure 2c). Radiation therapy was given to 4.3% of the patients (n=7, figure 2d). Two patients received other treatment modalities during pregnancy, such as imatinib (n=1) or radiofrequency ablation (n=1). In 42.6% (n=69) of patients, TOP or induction of labour (IOL) was carried out in order to start cancer treatment postpartum, with or without other treatment modalities being applied during pregnancy.

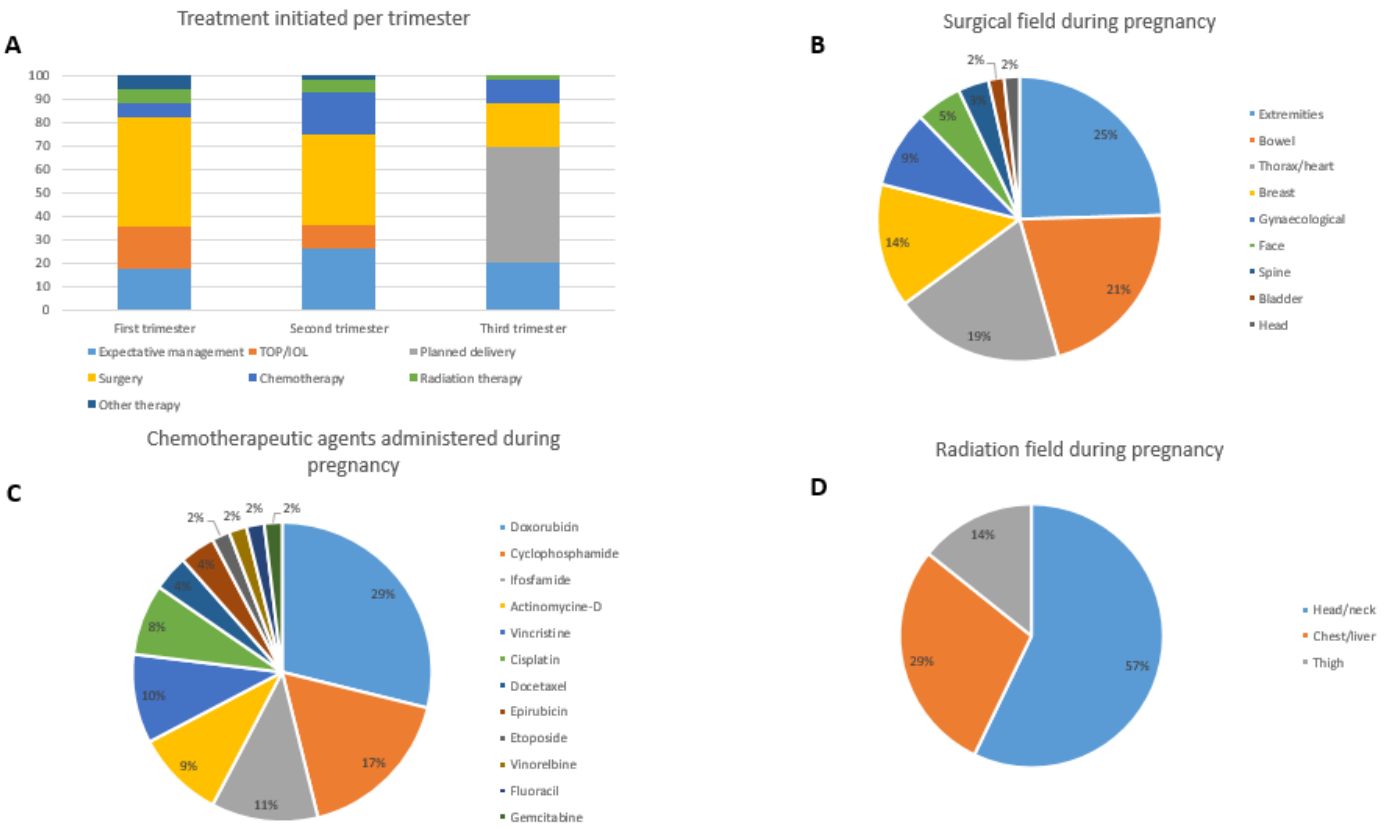


Figure 2 Overview of treatment administered during pregnancy. A: treatment initiated per trimester in percentages. *TOP = termination of pregnancy, IOL = induction of labor.* B: surgical field during pregnancy (n=63). C: chemotherapeutical agents administered during pregnancy (n=52) D: radiation field during pregnancy (n=7).

Of the 147 patients with known data on the outcome of pregnancy, 83.0% had a live birth (n=122), 9.5% had a TOP (n=14), 3.4% had a stillbirth (n=5) and 2.0% a late miscarriage (n=3, table 1). Of the eight patients who lost the pregnancy, one was receiving chemotherapy (vincristine, ifosfamide, doxorubicin, and etoposide) at the time of stillbirth, with chemotherapy starting at 15 weeks of gestation and the stillbirth occurring at 23 weeks of gestation. One patient lost her neonate due to massive haemorrhage and haemorrhagic shock during a laparotomy at 25 weeks of gestation. One patient had a stillbirth at 22 weeks of gestation, six weeks after small bowel surgery, and five patients did not receive any treatment before the pregnancy loss occurred. Three cases included from literature described pregnancies that were still ongoing at the time of analysis (2.1%). Pregnancies ended by elective caesarean section in the majority of cases (56.3%; n=63), followed by induction of delivery in 22.3% (n=25) and spontaneous birth in 21.4% (n=24). Among all live births, 65.2% were preterm (n=75). The median gestational age at delivery for all live births was 35 weeks (IQR 32-37). Of all preterm deliveries, 88% were induced preterm delivery (n=66), either by caesarean section or by medical IOL. Of these induced preterm deliveries, 66.7% (n=44) was induced for oncological treatment planning reasons. Of the other nine spontaneous preterm births that occurred between 25 and 36 weeks of gestation, six had received chemotherapy during pregnancy, with three patients also undergoing surgery. One patient had undergone surgery during pregnancy and two had received no treatment during pregnancy.

The median birth weight of the neonates was 2375 grams (IQR 1850-3001, table 1). There were three neonates with a congenital malformation (3.8%), more specifically an unspecified heart defect, an atrial septal defect and a multi-cystic dysplastic kidney. None of these mothers received cancer treatment during pregnancy. Two cases of placental metastasis were reported in the literature. One of these cases had a high-grade spindle cell sarcoma of the left lung of unknown stage and the other had a metastatic epithelioid sarcoma of the right fifth digit.

Of all patients for whom follow-up information was available (84%, n=136), 43.4% had a recurrence during follow-up (n=49) and 38.2% died (n=52, table 1). Follow-up time varied widely per patient, with a median of 22 months (range 0-160). Twelve case reports only mentioned maternal outcomes within six months after birth, while the remaining cases covered outcomes beyond six months. Among patients with known metastatic disease during pregnancy, 65.5% died (n=19) during follow-up.

DISCUSSION

This study represents the largest collection of patients with sarcoma in pregnancy, combining a previously unpublished collection of 45 patients registered in the INCIP database and 117 cases identified in a systematic review of existing literature. Twenty-five percent of all patients had metastatic disease at diagnosis. In nearly half of the patients, delivery was induced to enable initiation of cancer treatment,

with most live births being preterm. Most patients received surgery during pregnancy, followed by chemotherapy. Almost half of the patients experienced a recurrence, and 38.2% died with a median overall survival of 22 months.

According to the Surveillance, Epidemiology, and End Results (SEER) program for cancer statistics in the United States, approximately 16-18% of women between 15 of 50 years of age diagnosed with sarcoma have distant metastases, which is lower than the 25.6% described in our study population. [27] The general five-year relative survival rate for women under 50 with sarcoma is 75-77% (based on different tumour subtypes) and 27-44% in case of distant metastases. Younger age is associated with better survival. SEER does not specifically mention cancer diagnoses during pregnancy. With a mortality rate of 38.2% in our study population and 65.5% in our group of patients with metastases, the included pregnant patient population has a poorer outcome. While the number of patients per subtype in our study might be too small to draw conclusions about their prognosis, these findings may partly be explained by a delay in diagnosis or treatment initiation due to the concurrent pregnancy. Alternatively, we cannot exclude selective publication of cases with poor prognosis in the literature, resulting in an exaggerated estimate of the resulting mortality.

The symptoms reported during initial presentation in our study population largely depended on the location of the tumour. Some symptoms, such as oedema, bowel problems and vomiting, mimic pregnancy-related symptoms. As has been noted previously for breast cancer and gastrointestinal tumours, this may be a cause of delay in diagnosis. [28,29] It is important for physicians to be aware of the occurrence of cancer in pregnancy and the potential impact of delay in diagnosis on the maternal prognosis.

Most chemotherapeutic agents indicated for sarcoma can be administered during pregnancy, excluding MTX. As 17% of all patients in our study were treated with systemic therapy during pregnancy, including one patient treated with chemotherapy in the first trimester, it is reassuring that no treatment-related congenital malformations were reported. Oligohydramnios nor long-term adverse events in the children exposed to chemotherapy in utero were described in our study population, but follow-up was short in some patients treated with chemotherapy so information on long-term adverse outcomes in the child might be missing. Awareness of chemotherapy related fetal complications is necessary and requires the involvement of a perinatologist for appropriate follow-up of the child after delivery.

Radiation therapy was only administered in seven patients in our study. This might be explained by the reported fetal risks of radiation exposure above 100 mSv, but a recent paper by Van Assche et al. reported promising outcomes of children exposed to radiation therapy in utero, suggesting possibilities for future patients needing tailor made treatment plans involving radiation therapy. [30] Novel treatment

modalities like proton therapy or NTRK inhibitors were not administered in our pregnant study population.

Preterm births in our study population were mainly induced deliveries, and 60.6% of all preterm births were induced for oncological treatment planning reasons. Several papers have shown that there is a strong association between prematurity and poor neonatal and later life outcomes, regardless of in utero exposure to chemotherapy. [31,32] Seven patients in our study had a late miscarriage or stillbirth. Three of them could be caused by the oncological treatment the patient got before the pregnancy loss, but the other four were not related to treatment modalities. A poor maternal condition due to the cancer may contribute, although this is difficult to prove at this time. As more evidence emerges regarding treatment options during pregnancy, it becomes more evident that initiating treatment during pregnancy is important to improve maternal outcomes whilst trying to achieve a term gestational age for the child. However, for this group of patients with the observed poorer prognosis, outweighing the risks of treating the mother during pregnancy and inducing preterm delivery should be discussed in a multidisciplinary team on an individual patient level.

In our study population, two cases of placental metastases were identified without evidence of metastatic disease in neonates described. Wolters et al. published a review of the literature in 2021 describing 84 cases of placental metastases, mainly found in patients with melanoma, lung cancer and breast cancer. [33] Most cases of placental metastases are associated with metastatic disease (96.2%) and therefore with poor maternal outcome. In our collection of cases, one case of metastatic sarcoma and one case of sarcoma of unknown stage with placental metastases were described, underscoring the need to examine the placenta and check for metastases, especially in case of metastatic disease. It should be noted, however, that despite extensive pathological examination only 10% of the placental surface is examined, meaning the presence of (micro)metastases cannot be entirely ruled out. The discovery of metastatic disease results in upstaging of the condition and necessitates extensive examination and follow-up for the child.

Current recommendations for sarcoma in pregnancy are based mainly on general information about treatment modalities during pregnancy and case reports in the literature. The rarity of sarcoma in pregnancy makes multidisciplinary care essential. Most multidisciplinary teams (MDTs) treating sarcoma patients have limited knowledge of pregnancy, and the few known cancer in pregnancy MDTs do not have a sarcoma specialist on board. It is important to reach out to experts in the field for both staging as well as treatment related questions, and to link both cancer in pregnancy and sarcoma experts in this rare co-occurrence of sarcoma and pregnancy. Initiatives such as the Advisory Board on Cancer,

Infertility and Pregnancy (www.ab-cip.org) could help physicians caring for pregnant sarcoma patients by providing the most up-to-date recommendations on treatment options during pregnancy. [34]

CONCLUSION

Sarcoma in pregnancy is rare but does occur, as seen in this largest collection of sarcoma in pregnancy cases. The heterogeneity of the different tumour subtypes and the different symptoms make it difficult to formulate one set of recommendations. Prognosis of pregnant patients with sarcoma seems worse than of non-pregnant patients. Awareness on its occurrence and the large amount of possibilities of treatment during pregnancy may contribute to earlier diagnosis, decrease the number of preterm medically indicated inductions and hopefully improves maternal and fetal outcome.

REFERENCES

1 Gatta, G. *et al.* Rare cancers are not so rare: the rare cancer burden in Europe. *Eur J Cancer* **47**, 2493-2511 (2011).

2 Hui, J. Y. Epidemiology and Etiology of Sarcomas. *Surg Clin North Am* **96**, 901-914 (2016).

3 Brennan, M. F., Antonescu, C. R., Moraco, N. & Singer, S. Lessons learned from the study of 10,000 patients with soft tissue sarcoma. *Ann Surg* **260**, 416-421; discussion 421-412 (2014).

4 Papworth, K. E. *et al.* Soft-tissue sarcoma in adolescents and young adults compared with older adults: A report among 5000 patients from the Scandinavian Sarcoma Group Central Register. *Cancer* **125**, 3595-3602 (2019).

5 Ferrari, A., Dirksen, U. & Bielack, S. Sarcomas of Soft Tissue and Bone. *Prog Tumor Res* **43**, 128-141 (2016).

6 Stensheim, H., Møller, B., Van Dijk, T. & D., F. S. Cause-specific survival for women diagnosed with cancer during pregnancy or lactation: A registry-based cohort study. *Journal of Clinical Oncology* **27**, 45-51 (2009).

7 Johansson, A. L. V. *et al.* Cancer survival in women diagnosed with pregnancy-associated cancer: An overview using nationwide registry data in Sweden 1970–2018. *European Journal of Cancer* **155**, 106-115 (2021).

8 Strauss, S. J. *et al.* Bone sarcomas: ESMO-EURACAN-GENTURIS-ERN PaedCan Clinical Practice Guideline for diagnosis, treatment and follow-up. *Ann Oncol* **32**, 1520-1536 (2021).

9 Gronchi, A. *et al.* Soft tissue and visceral sarcomas: ESMO-EURACAN-GENTURIS Clinical Practice Guidelines for diagnosis, treatment and follow-up(☆). *Ann Oncol* **32**, 1348-1365 (2021).

10 Gamboa, A. C., Gronchi, A. & Cardona, K. Soft-tissue sarcoma in adults: An update on the current state of histiotype-specific management in an era of personalized medicine. *CA Cancer J Clin* **70**, 200-229 (2020).

11 Cipriano, C. A., Jang, E. & Tyler, W. Sarcoma Surveillance: A Review of Current Evidence and Guidelines. *J Am Acad Orthop Surg* **28**, 145-156 (2020).

12 Wolters, V. *et al.* Management of pregnancy in women with cancer. *International journal of gynecological cancer : official journal of the International Gynecological Cancer Society* **31**, 314-322 (2021).

13 Kal, H. B. & Struikmans, H. Radiotherapy during pregnancy: fact and fiction. *The Lancet. Oncology* **6**, 328-333 (2005).

14 Mazzola, R. *et al.* Modern radiotherapy in cancer treatment during pregnancy. *Critical reviews in oncology/hematology* **136**, 13-19 (2019).

15 Van Calsteren, K. *et al.* In utero exposure to chemotherapy: effect on cardiac and neurologic outcome. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology* **24**, e16-17 (2006).

16 van Gerwen, M. *et al.* Association of Chemotherapy Timing in Pregnancy With Congenital Malformation. *JAMA Netw Open* **4**, e2113180 (2021).

17 Vandenbroucke, T. *et al.* Child development at 6 years after maternal cancer diagnosis and treatment during pregnancy. *Submitted* (2020).

18 Van Calsteren, K. *et al.* Transplacental transfer of anthracyclines, vinblastine, and 4-hydroxy-cyclophosphamide in a baboon model. *Gynecol Oncol* **119**, 594-600 (2010).
19 Berveiller, P., Adam, J. & Mir, O. Feasibility of platinum-based chemotherapy during pregnancy. *Am J Obstet Gynecol* **199**, e21-22; author reply e22 (2008).
20 Verberne, E. A., de Haan, E., van Tintelen, J. P., Lindhout, D. & van Haelst, M. M. Fetal methotrexate syndrome: A systematic review of case reports. *Reprod Toxicol* **87**, 125-139 (2019).
21 Mir, O. *et al.* Doxorubicin and ifosfamide for high-grade sarcoma during pregnancy. *Cancer Chemother Pharmacol* **69**, 357-367 (2012).
22 Lambertini, M., Peccatori, F. A. & Azim, H. A., Jr. Targeted agents for cancer treatment during pregnancy. *Cancer treatment reviews* **41**, 301-309 (2015).
23 Bayer Pharmaceutical Inc. Vitrakvi (larotrectinib). November, 2018. https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/210861s000lbl.pdf (accessed March 15th, 2024)
24 Genentech. Rozlytrek (entrectinib). 2019. https://www.gene.com/download/pdf/rozlytrek_prescribing.pdf (accessed March 15th, 2024)
25 Moola S, M. Z., Tufanaru C, Aromataris E, Sears K, Sfetcu R, Currie M, Qureshi R, Mattis P, Lisy K, Mu P-F. in *JBI Manual for Evidence Synthesis.* (ed Munn Z (editors) Aromataris E) (JBI, 2020. Available from https://synthesismanual.jbi.global).
26 Tsakiridis, I., Mamopoulos, A., Athanasiadis, A. & Dagklis, T. Induction of Labor: An Overview of Guidelines. *Obstet Gynecol Surv* **75**, 61-72 (2020).
27 SEER*Explorer: An interactive website for SEER cancer statistics [Internet]. Surveillance Research Program, National Cancer Institute. https://seer.cancer.gov/explorer/ (Accessed 26th March 2024)
28 Boere, I. *et al.* Breast cancer during pregnancy: epidemiology, phenotypes, presentation during pregnancy and therapeutic modalities. *Best Practice & Research Clinical Obstetrics & Gynaecology* **82**, 46-59 (2022).
29 Lee, H. J. *et al.* Clinical characteristics of gastric cancer associated with pregnancy. *Dig Surg* **26**, 31-36 (2009).
30 Van Assche, I. A. *et al.* Long-term neurocognitive, psychosocial, and physical outcomes after prenatal exposure to radiotherapy: a multicentre cohort study of the International Network on Cancer, Infertility, and Pregnancy. *The Lancet. Child & adolescent health* **8**, 433-442 (2024).
31 Fischer, D., Ahr, A., Schaefer, B., Veldman, A. & Schloesser, R. Outcome of preterm and term neonates of mothers with malignant diseases diagnosed during pregnancy. *J Matern Fetal Neonatal Med* **19**, 101-103 (2006).
32 Van Assche, I. A. *et al.* Cognitive and Behavioral Development of 9-Year-Old Children After Maternal Cancer During Pregnancy: A Prospective Multicenter Cohort Study. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*, Jco2202005 (2023).
33 Wolters, V. *et al.* Placental pathology in cancer during pregnancy and after cancer treatment exposure. *Placenta* **111**, 33-46 (2021).
34 Amant, F., Heimovaara, J. H., Lok, C. A. R. & Van Calsteren, K. The Advisory Board on Cancer, Infertility and Pregnancy: a virtual on-demand multidisciplinary tumour board. *The Lancet Oncology* (2022).

Chapter 9 Guidelines on diagnosis and treatment of hematological malignancies during pregnancy

Daan Dierickx*, **Joosje Heimovaara***, Mar Bellido, Kristel Van Calsteren, Elyce Cardonick, Alvaro Cabrera Garcia, Adinda Baten, Andrew Evens, Andres Ferber, Monica Fumagalli, Elzbieta Lampka, Lena Specht, Vincent Vandecaveye, Ivan Vogelius, Markus Alber and Frédéric Amant

Submitted
* Contributed equally to the manuscript

ABSTRACT

The diagnosis and treatment of hematological malignancies during pregnancy has undergone significant advancements over the past few decades, resulting in enhanced outcomes. As possibilities continue to expand and the rising global incidence results in an increasing number of diagnoses within the pregnant population, there is a pressing need to gain a deeper understanding of the potential options for pregnant women and the impact on the newborn. As knowledge of the effects of cancer treatment increases, more women are receiving adequate cancer diagnosis and treatment during pregnancy. This necessitates the development of guidelines on the use of approved treatment modalities. This paper presents a summary of the use of diagnostic modalities and treatment options including chemotherapy, radiation therapy and immunotherapy for acute leukemia, Hodgkin lymphoma, non-Hodgkin lymphoma, myeloproliferative diseases, aplastic anemia and multiple myeloma during pregnancy.

INTRODUCTION

The worldwide incidence of hematological malignancies is currently projected to approximate 4.6 million cases in 2030. [1] While predominantly manifested in older patients, with a prevalence peaking among individuals aged 70 years and older, there are several major hematological malignancy subtypes seen during the reproductive years of the younger patient population. Acute lymphoblastic leukemia and Hodgkin lymphoma are most commonly diagnosed at an earlier age. Collectively, an estimated 15% of tumors associated with pregnancy are identified as hematological malignancies[2], predominantly characterized by lymphoma (occurring at an incidence rate ranging from 1:1000 to 1:6000 gestations), followed by leukemia (incidence of 1:75,000 to 1:100,000 pregnancies). [3]

Several guidelines regarding specific tumor types during pregnancy have been developed over the years, focusing on the most commonly occurring tumor types such as breast cancer and gynecological malignancies, and describing general treatment modalities. [4,5] The complex intersection of hematological disorders and pregnancy necessitates a pragmatic clinical framework. While there is a consensus advocating standard treatment during pregnancy whenever feasible, the daily management of women confronted with hematological malignancies still presents many dilemmas. The most recent guideline paper dates from 2016, and in the years since, treatment options have increased rapidly. [6] This guideline is based on case reports, retrospective series and expert opinion of several experts in the field of hematological malignancies worldwide.

GENERAL MANAGEMENT OF PREGNANT WOMEN WITH HEMATOLOGICAL CANCERS

Diagnosis and treatment of pregnant women presenting with hematological cancers is challenging as both the clinical status of mother and fetus need to be considered. To assure the best care possible, diagnostics and treatment plans should be discussed in a multidisciplinary team including hematologists, (radiation) oncologists, obstetricians, neonatologists, anesthesiologists and pharmacists, most preferably in a specialized referral center. [7] It is important to establish the precise clinic-pathological diagnosis including prognostic factors, and to determine curability, staging and comorbidities. [8] Treatment approaches must consider besides the efficacy also maternal toxicity, fetal teratogenicity and potential postnatal complications for the child.

Diagnosis and imaging

Diagnostics such as tissue sampling from bone marrow or lymphadenopathies for pathological diagnosis and molecular testing are identical as for the non-pregnant population (Figure 1). Imaging strategies for diagnosis and staging are usually tailored to balance maternal risk and diagnostic needs with fetal safety.

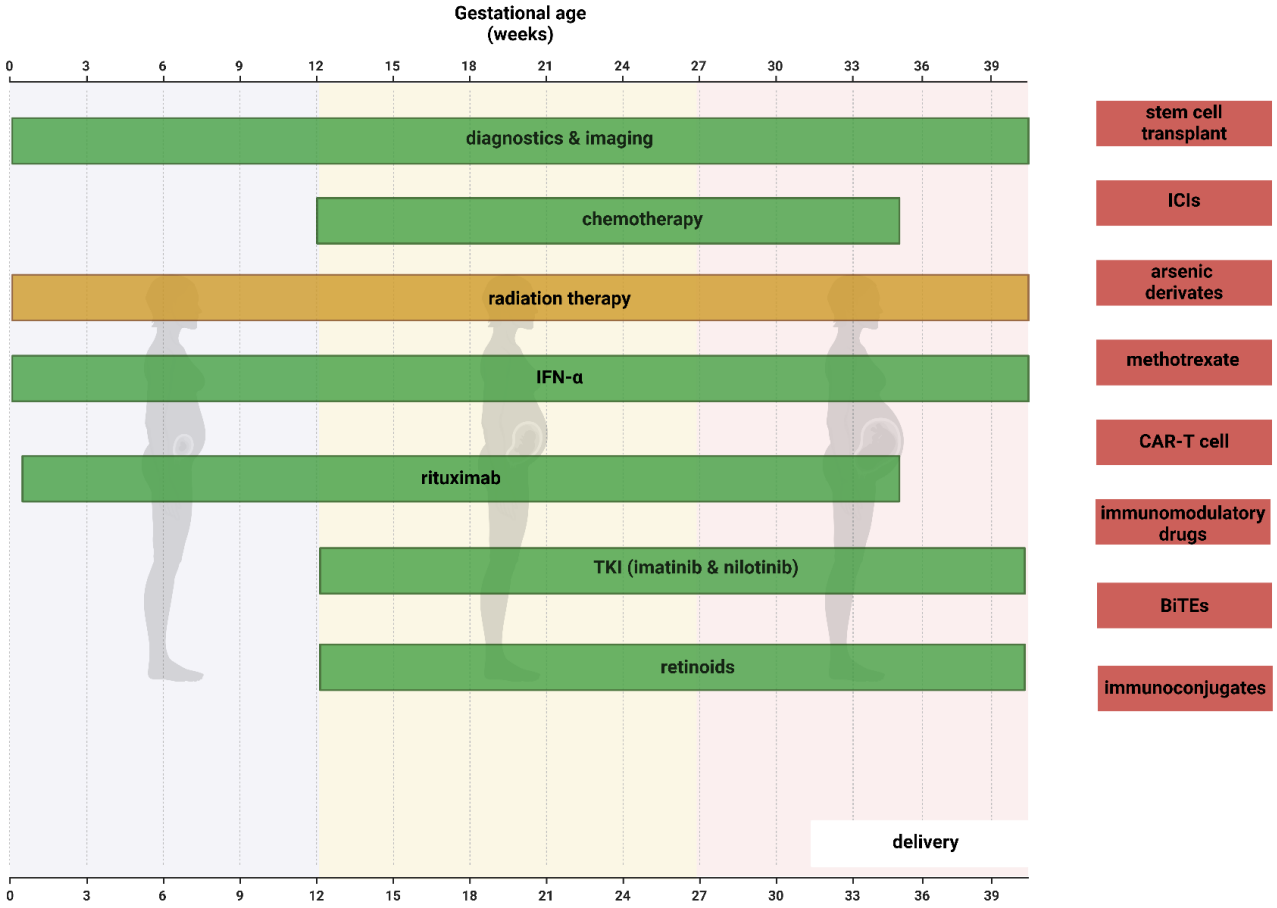


Figure 1. Overview of most common diagnostics and systemic treatment modalities during pregnancy. *green coloured box meaning possible, orange meaning possible under specific circumstances, red meaning contraindicated during pregnancy. Created with BioRender.com*

Ultrasound is appropriate as an initial screening tool in case of a palpable mass or lymphadenopathies and enables immediate image guided biopsy. [9] While chest X-Ray allows rapid initial screening in case of dyspnoea or to exclude a mediastinal mass, computed tomography (CT) examinations should be performed with intravenous iodinated contrast when indicated as it significantly improves the diagnostic information. For this purpose, nowadays, only low-osmolarity, water-soluble iodinated contrast agents should be used, which have never been related to cases of neonatal hypothyroidism. [10,11] Due to their high accessibility, ultrasound and CT remain the primary imaging modalities of choice for imaging suspected maternal complications and life-threatening complications.

For complete staging of haematological malignancy, Positron Emission Tomography (PET)/CT is not recommended as primary imaging modality during pregnancy. [6] Whole body magnetic resonance imaging with diffusion-weighted sequence (WB-DWI/MRI) is preferred over CT, the latter only to be used when MRI is unavailable. [9] WB-DWI/MRI basically consists of transverse DWI sequence stacks covering

the head to below the pelvis with coronal and sagittal reformatting with T2 and T1 whole body sequences as anatomical correlate. The DWI-sequence obviates the need for Gadolinium contrast and adds functional imaging properties to the MRI examination, enabling the detection of disease sites without anatomical disruption and functional response assessment in hematological malignancy. [12,13]

WB-DWI/MRI has shown higher per patient sensitivity for detecting bone disease in multiple myeloma and has similar impact on treatment decisions as PET/CT. [14] In lymphoma, WB-DWI/MRI has concordance of 99,4% with PET/CT for detecting nodal and extranodal lymphoma, while staging with both modalities has shown similar impact on progression-free survival and patient management. [15,16] WB-DWI/MRI also enables reliable interim and post-treatment response evaluation with reported agreement of 99.2% with PET/CT for predicting outcome. [17] Therefore, WB-DWI/MRI represents an accurate non-irradiating alternative to PET/CT for staging and interim response assessment of several hematological malignancies during pregnancy with the ability to guide therapeutic management. Importantly, the diagnostic information between WB-DWI/MRI and PET/CT is interchangeable meaning that PET/CT mostly replaces WB-DWI/MRI for end of treatment response assessment after birth. During pregnancy, PET/CT can be employed as a second line problem solving technique in case WB-DWI/MRI would produce equivocal results. However, this is rarely the case and should only be employed if the diagnostic problem is critical for maternal outcome.

As per American College of Radiology appropriateness criteria, abdominal shielding with a lead apron around the pelvis is not recommended for X-ray, CT or PET/CT examinations. CT scans outside the field of the fetus, expose the fetus only to negligible doses of scatter radiation. A phantom study has indicated that patient shielding in Chest CT for pulmonary embolism can increase the effective maternal and fetal radiation dose. [18] For CT-scans covering the field of the fetus, the introduction of the highly attenuating lead apron will force the CT-scanner to increase the tube current and radiation output in trying to penetrate the shield and acquire diagnostic images, increasing the radiation dose to the fetus.

Chemotherapy

Chemotherapy is often used as a first-line treatment for hematological malignancies. However, due to its minimal selectivity and its ability to attack rapidly proliferating cells, it carries a risk of teratogenic effects on the developing fetus. Transplacental transfer of most chemotherapeutic drugs occurs by passive diffusion and is influenced by factors such as molecular size, lipid solubility, protein binding, and ionization. [19] As most chemotherapeutic drugs have a low molecular weight and are uncharged and unbound, they can easily cross the human placenta. [20,21]

There is an association between exposure to chemotherapy before the 12th week of pregnancy and an increased risk of congenital malformations detected during pregnancy or after birth (Figure 1). [22]

This increased risk is most likely due to the disruption of organogenesis. However, after 12 weeks of gestation, the risk of congenital malformations decreases essentially to the standard population risk for most chemotherapeutics. Nevertheless, there is still a risk of intrauterine growth restriction, preterm birth, and small for gestational age at birth, underscoring the role of the perinatologist in the multidisciplinary team and the importance of accurately dating the pregnancy as early as possible. [2]

Because of the toxic effects of chemotherapy on the maternal bone marrow, and consequently on the fetal bone marrow as well, it is important to consider a specific window of time between the last chemotherapy administration and delivery to minimize the risk of maternal infections and bone marrow depletion in the child during and after birth. [23] In most cases this will result in a planned and coordinated delivery, which will allow for the timely resumption of further chemotherapy postpartum, if indicated.

Radiation therapy

Radiation therapy in the treatment of hematological malignancies is primarily relevant in the treatment of lymphomas. If an exceptional situation arises where radiation therapy cannot be avoided, there are a number of considerations (Figure 1). The risks associated with radiation vary according to the gestational age and the cumulative radiation dose to the fetus. The available data are from animal studies and from survivors of atomic disasters, primarily from Hiroshima and Nagasaki and from Chernobyl. As the quality of the radiation, dose rates etc. at the atomic disasters were different from therapeutic irradiation, the exact risks are somewhat uncertain. However, in the first trimester the risks of malformations and growth retardation are highest. They seem to occur at a threshold cumulative dose of 0.1 Gy, and the risk rises in a linear fashion with dose. [24,25] Hence, radiation therapy should only be used in exceptional cases in the first trimester. The risks are lower and the threshold higher in the second and third trimesters. However, there remains a risk for potential IQ decrease with radiation exposure up to 25 weeks of gestation. [26] Next to that, the risk of malignant disease in the offspring is, although minimally, elevated throughout pregnancy. This is a stochastic effect of radiation with no lower threshold and with a risk proportional to the cumulative dose to the fetus. [24,27] Recent prospective data on children born from mothers treated with radiation therapy during pregnancy indicate no neurocognitive, psychosocial or physical problems. Although numbers were small, follow up in some cases was long. [28] Larger data materials with longer follow-up of all cases are needed to draw more solid conclusions.

Quantification of low, out-of-field doses to the fetus is important but requires specialized knowledge and careful consideration of the individual case. Fetus dose originates from leakage of radiation from the treatment machine, scattered radiation from components (collimators, filters) within the beam

path, and from scatter within the patient. Additionally, the dose from the imaging procedures should be considered. The main factors affecting the fetus dose are presented in brief in Table 1. Commercial dose planning systems cannot be relied upon to provide accurate estimates of the low dose contributions at a distance from the main treated area. Therefore, the most important recommendation is that each case should be reviewed in collaboration between treating physician and a medical physics expert, possibly using Table 1 as a starting point. We recommend simulation or phantom measurements adapted to the individual case and consideration of additional shielding over the abdomen, albeit with consideration of the mechanical risk of the heavy blocks. [25]

SOURCE	EFFECT	IMPORTANCE FOR FETUS DOSE	MAIN EFFECTS INCREASING FETUS DOSE	RECOMMENDATIONS
Therapeutic beam	Scatter outside patient	High	Any material in primary beam path will increase dose	Carefully consider the material in beam path. Simulate effect if "more than an accessory tray".
	Within patient scatter ("Phantom scatter")	High	Larger fields, smaller distance to fetus, high maternal BMI, and higher photon energy will increase dose. Fetus dose from phantom scatter essentially proportional to prescription dose times volume of target.	Prefer unflattened beams. Avoid wedges. Prefer intensity modulated techniques. Avoid passive scatter protons. Do not use photon energies higher than 6 MV Minimize number of monitor units, e.g. by using simpler techniques. Perform individual risk assessment, simulation and/or measurement
	Leakage dose	Medium	Older accelerator designs may have poorer shielding leading to higher doses	Treat on the best shielded machine available
Imaging	Leakage from generator	Medium	Shielding designs of onboard imagers and image intensity	Use 2D imaging for positioning if possible. Alternatively use dose-sparing cone beam techniques. Measure leakage from generator. Consider using lead apron.
	Within patient scatter	Low	Out-of-field scatter of kV image energies has short range and is scattered away from fetus.	Additional MV irradiation for imaging should be avoided.

Table 1. Contributions to fetal dose from radiation therapy procedures. *BMI: Body Mass Index; MV: megavolt; 2D: two dimensional; kV: kilovolt*

Proton therapy has been suggested as giving a lower dose to the fetus than photon therapy. [29] With protons the main contribution to the dose to the fetus comes from the production of neutrons in the beam shaping accessories, which is much higher with scattering technique than with spot scanning. [24,25,30,31]

Targeted therapy and immunotherapy

Targeted therapies are a diverse range of drugs, including among others rituximab, tyrosine kinase

inhibitors (TKIs) such as BCR-ABL inhibitors, and immunotherapeutic agents including checkpoint inhibitors (ICIs), antibody-drug conjugates (ADCs), bispecific T-cell engagers (BiTEs) and chimeric antigen receptor T-cell (CART) therapies. These therapies target molecules or pathways involved in the growth and survival of cancer cells and are increasingly being used to treat hematological malignancies. Targeted agents are designed to specifically target (tumor-related) proteins, which may also have physiological roles in fetal or placental development. [32] Therefore, their effects on fetal and placental development need to be carefully assessed.

The transplacental transfer of drugs is affected by their molecular size. Large molecules, such as monoclonal antibodies like rituximab or immune checkpoint inhibitors (ICIs), require active transport facilitated by FcRn receptors. [33] This active transport mechanism does not occur until 14 weeks of pregnancy and gradually increases during the second and third trimesters. Therefore, the risk of congenital malformations is relatively low, but there is a risk for intrauterine growth restriction and premature rupture of membranes, as frequently seen in patients treated with ICIs during pregnancy. [32]

Rituximab is a drug used to treat CD20-positive B-cell lymphomas, acute B-lymphoblastic leukemia and CLL. [34] When administered during pregnancy, it is associated with short-term cytopenia and B-cell depletion of the neonate at birth. [35] A paper by Maggen et al. described 36 pregnant patients with non-Hodgkin lymphoma who received rituximab, resulting in 13% cases with neonatal complications and 8% with maternal infections. [36] Considering the available information, the advantages of using rituximab for hematological malignancies during pregnancy appear to outweigh the potential risks for both the mother and child (Figure 1). However, it is important to carefully consider the potential risks of neonatal infection due to cytopenia.

BRC-ABL inhibitors, including imatinib, dasatinib and nilotinib, are TKIs used to treat Philadelphia chromosome-positive CML, ALL, and chronic eosinophilic leukemia. [34] TKIs are small molecules that can cross the placenta from the first trimester onwards, and therefore, their administration during the first trimester of pregnancy is associated with congenital anomalies, with reported malformations including skeletal defects with or without urogenital malformations, with a known prevalence for imatinib of around 11%.[37-39] Additionally, there are high rates of spontaneous abortion, ranging from 12% to 25%.[35] Hydrops fetalis was also reported after dasatinib exposure. [40] Imatinib and nilotinib have the lowest transplacental transfer rate compared to dasatinib. [37,41] Both imatinib and nilotinib have been safely administered during pregnancy after the first trimester (Figure 1).

Finally, when using immunotherapy, the risk of immune-related adverse events (irAEs) must be considered. The literature shows examples of not only the risk of an irAEs for the mother and pregnancy

itself but also the risk for the child to develop severe irAEs after birth due to exposure to immunotherapy *in utero.* [42,43]

MANAGEMENT OF SPECIFIC HEMATOLOGIC CANCERS IN PREGNANCY

Acute Leukemia

1. Acute leukemias are usually reported during the second (37%) and third trimester (40%) versus the first trimester (23%, including miscarriages). [44-46]

2. Both diagnosis and monitoring of minimal residual disease should be performed as by any other acute leukemias outside the context of pregnancy.

3. Treatment initiation should not be delayed, as delay significantly decreases the chance of remission and increases the mortality associated with leukemia progression for both mother and fetus. [46-48]

4. In case of hyperleukocytosis (leukocytes >100x 10^9/L) leukaphereses is currently not recommended because it does not improve survival, instead, start immediately methylprednisolone (for ALL) and/or cytoreductive chemotherapy (for AML) as outside of pregnancy. [49,50]

5. For patients who are diagnosed in the first trimester, elective termination of pregnancy could be a good choice to be able to offer maximal treatment to the mother. Elective abortion is contraindicated in case of disseminated intravascular coagulation (APL, monocytic leukemia) and should be delayed till correction of disseminated intravascular coagulation. In cases where the mother does not want to have an elective abortion during the first trimester, treatment as outside pregnancy is recommended after having consulted the ethical commission of the institution and haven given the risk of malformations and spontaneous abortion to the mother if treatment is accepted.

6. As chemotherapy for leukemia induces deep pancytopenia and takes a month to recover (at least for cytarabine/daunorubicine), chemotherapy should not be started later than 34 weeks of gestation. Between 30 and 32 weeks of gestation, the discussion to start chemotherapy or to perform induced delivery should be discussed with the patient taking into account the blood counts at that time. At 32 weeks of gestation or later, induced delivery before starting chemotherapy could be a good choice for better outcomes. [7,51] In case of disseminated intravascular coagulation, induced delivery should be delayed until correction.

7. For patients diagnosed during the second or early in the third trimester, recommended treatment is the same as in non-pregnant women avoiding some teratogenic drugs (see table 2).

Pregnant women during infusion of chemotherapy and/or rituximab may experience preterm contractions, making obstetrical monitoring mandatory during immuno-chemotherapy treatment.

ALL	Use of ALL pediatric inspired regimens (AYA protocols). Omit methotrexate to avoid the aminopterin syndrom. [52] Use methylprednsiolone instead of dexamethasone (no placenta transfer). Use of daunorubicine is allowed during pregnancy. [53] Asparaginase is not recommended during pregnancy due to a high frequency of thrombotic events. [54] Rituximab can be used safely but monitoring of B-lymphopenia in the neonate during the first 6 months is needed. [55] Tyrosine kinase inhibitors: nilotinib is preferred as it crosses the placenta the least. [37] Blinatumomab and inotuzumab ozogamycin should not be used during pregnancy unless the potential benefit outweighs the potential risk to the foetus. Allogeneic stem cell transplant is lethal for the fetus and should be postponed after the delivery.
AML	Initiation of '3+7' (daunorubicin + cytarabine) should be started without delay after 12 weeks of gestation. Standard bone marrow aspiration on day 15 after chemotherapy to see if the AML is chemo-sensitive, is recommended. Consolidation with high doses cytarabine should be given as in non-pregnant women. [51,53] Allogeneic stem cell transplant is lethal for the fetus and should be postponed after the delivery. In patients initially unable to receive intensive chemotherapy, low-dose cytarabine or azacytidine combined with venetoclax could be an option, based on expert opinion. Venetoclax has been reported to be used in 1 case with success during the 2nd trimester of pregnancy combined with mitoxanthrone and high-dose cytarabine in a chemo-refractory AML. [56] Azacytidine has been reported to be used with success in 2 cases during the 3rd trimester. [57,58] FLT3 inhibitors are not recommended during pregnancy.
APL	Retinoids are highly teratogenic. [59] Arsenic derivates (ATO) are highly embryotoxic and contraindicated during the whole pregnancy. [60,61] During first trimester: ATRA is contraindicated and if there is no wish for an interruption of the pregnancy, daunorubicine monotherapy is advised. During second and third trimester: combination of ATRA and chemotherapy (daunorubicine) is relatively safe taking into account that monitoring of the cardiac function and growth of the fetus is strictly recommended.
Indolent lymphoma	Non abdominal stage I or II contiguous consider observation or low dose radiation therapy (4 Gy) in cases with an indolent course. If symptomatic, change to standard dose with curative intent. Gastric MALT lymphoma antibiotic trial Advance stage: low tumor burden or high tumor burden asymptomatic observation high tumor burden symptomatic rituximab single agent, or R-chemotherapy, or steroid bridge (second and third trimester)
Aggressive lymphoma	First trimester pregnancy termination Second and third trimester Diffuse large B cell lymphoma R-CHOP or R-EPOCH if double hit lymphoma. Primary mediastinal B cell lymphoma R-CHOP could consider DA R-EPOCH Burkitt lymphoma could consider DA R-EPOCH or more intensive regimens without antimetabolite before week 20.

Table 2. specific treatments in newly-diagnosed acute leukemias & NHL.

Hodgkin Lymphoma

1. Hodgkin lymphoma (HL) presents at a frequency of 0.7 to 8.1 cases per 100,000 births, equating to about 1 in 1,000 to 6,000 pregnancies. In 3.2% of all HL patients, a pregnancy is coexistent. [2,8,62]

2. Many cases of pregnancy-associated HL present in early-stage IA/B or IIA. [8,63]

3. Deferral of treatment until after the first trimester is possible for cases of asymptomatic or symptomatic early-stage HL (Figure 2). Termination of pregnancy in the first trimester may be considered if treatment cannot be delayed and acute fetal toxicity is a concern. [6,45,64] Delayed treatment start until the first trimester may adversely affect survival for pregnant women with symptomatic advanced HL. Use of steroids may facilitate bridging to the second trimester.

4. Deferral of treatment, especially for asymptomatic patients with low tumor burden, may be preferred when childbirth is imminent and postpartum therapy can be administered without significant delay. [62] Symptomatic patients could use pulse steroids and/or single-agent chemotherapy (vinca-alkaloids preferred). [62,65,66]

5. Deferral of treatment until after delivery is possible for cases of asymptomatic or symptomatic early-stage HL. [67] However, patients should be followed closely for potential progressive disease to avoid harmful effects to the fetus or mother. Where possible, the overarching goal should be a full-term delivery.

6. For advanced-stage HL patients with significant symptoms and/or high tumor burden, there is evidence that supports the safety and efficacy of ABVD given beyond the first trimester of pregnancy, as early as 13 weeks of gestation (table 3). [8,63,68]

7. The ADC brentuximab vedotin, is contraindicated in pregnancy due to potential fetal toxicity.[69]

8. There are no reports of BEACOPP use during pregnancy. [45]

9. Combined modality therapy involving chemotherapy and RT is generally not recommended during pregnancy.[70]

10. Administration of ICIs during pregnancy is described in a few cases in the literature. One report by Evens et al described the use of nivolumab from 26 through 37 weeks of gestation for relapsed/refractory Hodgkin lymphoma with positive outcomes for the child and mother after further therapy postpartum. [71]

11. The safety of employing RT with abdominopelvic shielding has been evidenced in patients with favorable early-stage HL and supradiaphragmatic disease, including the cervical, occipital, and axillary regions. [72] Fetal radiation exposure remains minimal with precautions, typically below 0.2 cGy.

12. Low-dose RT could be considered for isolated, symptomatic supradiaphragmatic disease as a bridge to postpartum chemotherapy. [73]

13. Limited data exists on relapsed/refractory HL during pregnancy. [71,74]

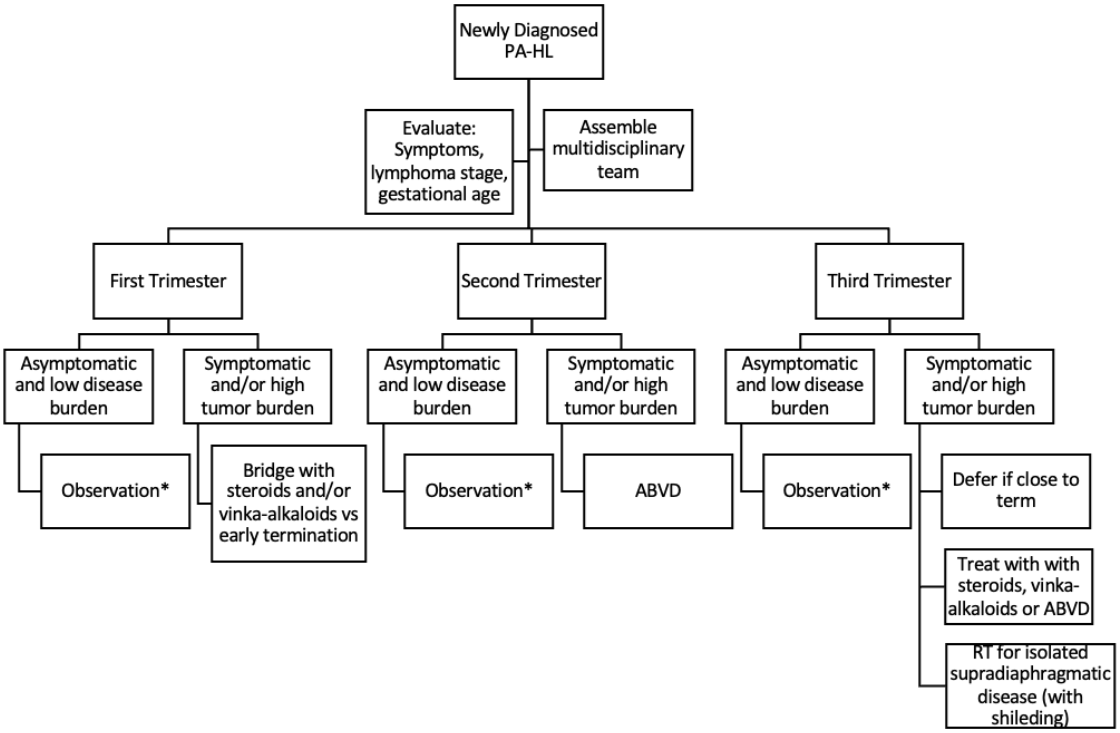


Figure 2. Therapeutic paradigm for pregnancy-associated newly diagnosed Pregnancy Associated Hodgkin lymphoma (PA-HL). *Abbreviations: ABVD = Doxorubicin, Bleomycin, Vincristine, Dacarbazine; RT radiation therapy. *When deferred therapy is not thought to negatively impact maternal prognosis (i.e., evaluate risks of treatment vs risks of no treatment)*

ARTICLE	SIZE	TREATMENT	SURVIVAL OUTCOMES	OBSTETRICAL OUTCOMES	FETAL OUTCOMES
MAGGEN ET AL. LANCET 2019 [68]	N= 134 pregnant patients with HL; n=101 (75%) stage I-II disease	72 (54%) antenatal ABVD; 56 (42%) deferred Rx; RT only in 6 (4%)	Early: 5-year PFS: 83%, OS: 97.3% Advanced: 5-year PFS: 91%, OS: 100%*	Preterm contractions in 12%, PROM in 5% exposed to antenatal Rx	Outcomes similar for those exposed to antenatal Rx vs. unexposed; 4 (3%) major congenital anomaly
PINNIX ET AL. JAMA ONCOL 2016 [63]	N= 39 pregnant patients (31 HL; 8 NHL); n=32 (82%) stage I-II disease	24 (61%) antenatal Rx (chemo and/or RT); 12 (31%) deferred Rx until postpartum	5-year PFS: 75%, OS: 82% (no difference in outcome based on timing of Rx)	Preterm delivery in 7 (29%) exposed to antenatal Rx	Antenatal Rx group: 4 miscarriages (2/4 in 1st trimester); No fetal abnormalities
EVENS ET AL. JCO 2013 [75]	N= 90 pregnant patients (40 HL; 50 NHL); n=54 (60%) stage I-II disease	56 (67%) antenatal Rx (chemo and/or RT), 66% antenatal Rx, 28 (33%) deferred to postpartum	HL 3-year PFS: 85%, OS: 97%;	Preterm delivery 26 (44%), PROM in 13% (*P= .07)*, pre-eclampsia 7% (*P= .06)*, C-sections 44% NHL pts vs. 19% HL (P= .007)	47 (56%) full term gestations; similar outcomes between antenatal vs. deferred Rx groups; 1 microcephaly, 1 pelvicactasis
VAN CALSTEREN ET AL. JCO 2010 [76]	N= 215 pregnant patients (13 HL; 10 NHL)	122 (56.7%) antenatal Rx, 28 (27%) received postpartum Rx	Not available	71% pregnancies induced; Preterm labor increased by 12% (*P= .120*) in antenatal Rx group	54% preterm; 24% (P=.001) low birth weight in antenatal Rx group; no increased incidence of congenital malformations

Table 3. Summary of Maternal, Obstetrical, and Fetal Outcomes for Pregnancy Associated Lymphoma**.** *Abbreviations: HL=Hodgkin Lymphoma; NHL=Non-Hodgkin Lymphoma; ABVD= doxorubicin, bleomycin, vinblastine, dacarbazine; Rx=Treatment; RT= radiation therapy; Chemo=chemotherapy; PFS=progression free survival; OS=Overall Survival; PROM=preterm rupture of membranes; C-section=cesarean section*

Non-Hodgkin lymphoma

1. Diffuse large B-cell lymphoma (DLBCL) is the most frequently occurring subtype during pregnancy. [8,77]

2. The decision to administer antenatal therapy is based mainly on the following factors: type of NHL (indolent vs aggressive, symptomatic vs non symptomatic), gestational age, and patient preference.

3. Asymptomatic patients with low tumor burden indolent NHL may be observed, whereas aggressive subtypes warrant systemic therapy in many patients, especially if diagnosed in the 2nd or early 3rd trimester (table 2).

4. Combination chemotherapy, although relatively safe during the second and third trimesters is contraindicated before 12 weeks of gestation. [22,78]

5. Rituximab-CHOP has been the standard of care therapy for patients diagnosed with DLBCL. In a cohort study by Maggen et al. that reported the outcomes in 80 pregnant patients with NHL, 89% received R-CHOP. [36] The 3-year progression-free and overall survival for patients with DLBCL treated with R-CHOP was 83·4% and 95·7% for limited stage and 60·6% and 73·3% for advanced stage. These results indicate the feasibility or R-CHOP in pregnant women with lymphoma. Another study has shown similar results and an overall survival rate at 5 years of 82% for DLBCL and primary mediastinal B cell lymphoma with favorable neonatal outcomes. [79] The CPI polatuzumab vedotin added to a CHOP-like platform is now FDA approved in non-pregnant patients. [80] However, the safety of this agent given antenatal, as well as other ADCs, is unknown and currently not recommended.

6. NHL warranting antimetabolite therapy (primary CNS lymphoma and Burkitt lymphoma) is challenging during pregnancy. [81,82] Aggressive chemotherapy regimens including antimetabolites during pregnancy have been reported. However, caution is advised regarding fetal teratogenicity (methotrexate [MTX] syndrome and myelosuppression). Hence, they are not recommended. Recent experience using DA-EPOCH-R in non-pregnant patients with Burkitt lymphoma and other highly aggressive lymphomas may provide an antimetabolite-free regimen for some pregnant patients with this disease. [83]

Myeloproliferative neoplasms

1. Myeloproliferative neoplasms (MPN), in particular Philadelphia (Phi)-positive chronic myeloid leukemia (CML), essential thrombocytopenia (ET) and to a lesser extent polycythemia vera (PV) are often diagnosed among younger patients.

2. ET is the most common MPN in women of childbearing age and is associated with an increased risk of thrombosis. In general this risk is estimated based on a history of thrombosis, the presence of a JAK2V617F mutation, older age and other cardiovascular risk factors. [84] In addition, caution is warranted in pregnancy given its association with a pro-coagulant state.

3. Despite several older retrospective series have shown less favorable maternal and fetal outcome in Phi-negative MPN, recent studies including substantial numbers of pregnant patients clearly show improving trends in both live birth rates and maternal thrombotic complications. However, preterm birth and requirement of temporarily care on a neonatal care-unit are observed commonly and warrant caution. [85-88]

4. Low dose aspirin should be given in all patients with ET and PV during the pregnancy, unless absolutely contra-indicated, as this is associated with better maternal and neonatal outcome. [89]

5. In high-risk patients necessitating cytoreductive therapy, hydroxycarbamide (hydroxyurea) and anagrelide are contra-indicated throughout the pregnancy. In these cases IFN-α can be given targeting platelet counts and hematocrit similar to non-pregnant MPN patients. [90,91]

6. The use of prophylactic dose of low molecular weight heparins (LMWH) is indicated in patients presenting with additional risk factors, in particular other cardiovascular risk factors or prior thrombosis. [88,90,92]

7. If necessary, intermittent venesections can be offered to pregnant PV patients to decrease hematocrit to safe ranges.

8. For CML, the tyrosine kinase inhibitors imatinib and nilotinib seem to be safe and effective in second and third trimester as their crossing through the placenta is limited. [37,41,93,94]

Aplastic anemia

1. Aplastic anemia is a rare clonal disorder, manifesting with variable degree of bone marrow suppression, ranging from non-severe (nsAA), severe (sAA) to very severe (vsAA). [95]

2. Association with pregnancy is possible, but it remains unclear if pregnancy increases AA risk.

3. Depending on severity, treatment consists of combination of supportive care with transfusion, thrombopoietin receptor agonists (TPO-RA), immunosuppressive therapy and allogeneic transplantation. [95]

4. Supportive care with transfusion, in particular platelets, are considered standard of care and allow to delay more intense therapy until after delivery. Recently, the TPO-RA eltrombopag has been approved for the treatment of aplastic anemia. TPO-RA have been used in pregnant patients with immune thrombocytopenia (ITP) and seem to be safe in the second and third trimester. [96-98]

5. If immunosuppressive therapy is needed, cyclosporine A can be given during pregnancy, although association with premature delivery and small for gestational-age infants have been described. [99]

6. ATG and allogeneic hematopoietic stem cell transplantation are contra-indicated during pregnancy and should be delayed until after delivery.

7. For women with history of aplastic anemiapreviously treated with immunosuppressive therapy, uncomplicated pregnancy is possible, although incomplete remission (in particular low platelet counts) is a risk factor for complications affecting mother or fetus. [100]

8. In case of presence of a paroxysmal nocturnal hemoglobinuria clone, treatment with eculizumab should be considered to minimize the risk for thrombosis and miscarriage. [101]

Multiple myeloma

1. The incidence of multiple myeloma in pregnancy is not clear, however when they coincide, it is recommended to start immediate treatment to avoid possible complications associated with myeloma and those derived from compression of the spinal canal due to occupying lesions. [102,103]
2. It is recommended to start with steroids, preferably methylprednisolone or prednisolone as it is known that dexamethasone (the steroid of choice in multiple myeloma) is less preferred in pregnancy. [104] The use of thromboprophylaxis and early identification of infectious processes is mandatory.
3. The drugs that cause less damage to the fetus, and maintain adequate antineoplastic activity are cyclophosphamide, doxorubicin, vincristine, which could be combined with steroids to temporarily reduce and "control" the tumor burden. [105]
4. The following drugs are contraindicated during pregnancy: daratumumab, carfilzomib, bortezomib, melphalan, thalidomide, lenalidomide, pomalidomide, and there is little knowledge about new biological drugs in the context of pregnancy, and tha- and lenalidomide known to be a teratogen. [103] When facing pregnant multiple myeloma patients at early gestational ages needing these drugs, a termination of pregnancy can be considered for optimal maternal prognosis.
5. Bisphosphonates to prevent myeloma-related skeletal events can be used during pregnancy without increased risk for serious fetal adverse events.[106]
6. Decreasing tumor burden by administering steroids as soon as possible and adding cyclophosphamide weekly or monthly to increase antineoplastic potency is recommended.[107,108]
7. It is preferred to delay delivery or cesarean section after the 37th week of gestation, taking also into account potential disease involvement of the spine and subsequent risk for pathological fractures with regards to mode of delivery.
8. We do not recommend starting treatment in case of monoclonal gammopathy of undetermined significance or smoldering multiple myeloma.[109]

OBSTETRICAL CARE

Compared to locoregional tumors, hematological cancers, in particular acute leukemia, have a systemic impact. They interfere with the hematological and cardiovascular requirements for adequate placental perfusion, oxygen and nutrient exchange. Adequate and immediate disease control improves both the maternal, obstetrical, and neonatal outcome.[110]

Hematological cancers increase the risk of gestational complications

Suboptimal placental blood flow (increased resistance of uteroplacental vessels, insufficient concentration gradient) and functional or placental inflammatory reactions result in fetal growth restriction, preterm labor and stillbirth. Anemia, thrombocytosis and leukocytosis (increased thrombosis), diffuse intravascular coagulation, maternal nutritional deficiencies and hypoxia may also affect fetal health. [111]

Thrombocytopenia increases the risk of bleeding complications (miscarriage, abruption, antenatal placental bleeding associated with growth restriction and preterm labor, postpartum hemorrhage). Leukopenia increases the vulnerability for infections associated with preterm labor, growth restriction in case of (inter)villositis, fetal (and early neonatal) sepsis in case of maternal sepsis or chorioamnionitis, and congenital infections.

When the placentas are examined from pregnancies complicated by hematologic malignancy, intravillous involvement can occur with reported frequencies between 22 and 50%.[112,113] Fetal metastasis (7.8%, n = 6) are most commonly reported in women with melanoma (n = 4), but have been reported with lung cancer and non-Hodgkin lymphoma. Among the cases with placental involvement and known infant outcome (n = 83), the majority of live born offspring had no evidence of disease at birth or during follow up (79.5%).[114]

When chemotherapy is administered during the first trimester, congenital anomalies are significantly increased. Exposure in the second and third trimester of pregnancy is associated with fetal growth restriction, preterm birth and stillbirth, with the last complication mostly concentrated in acute leukemia rather than lymphoma. These complications can occur with acute leukemia even without therapy. Chemotherapy in the third trimester is associated with neonatal hematopoietic suppression (Table 4). [115]

MATERNAL CANCER TYPES	N NEWBORN ENROLLED	N NEWBORN EXPOSED TO CHEMO	CONTROL GROUP	STUDY PERIOD	SHORT-TERM OUTCOME	LONG-TERM OUTCOMES		AUTHOR
						Age at assessment and tests	Findings	
VARIOUS (5 ALL, 2 AML, 7 HL, 4 NHL)	70	70	no	INCIP database 1991-2011	Median GA (weeks) at birth: 35.7 (range 28.3-41)	Bayley scale at 18, 36 months	Median follow-up age 22.3 months	Amant et al. [116]
						Wechsler scale at 5-6, 8-9, 11-12, 14-15 and 18 years	Cognitive performance comparable to general population normative data	
						ECG and electrocardiography	Prematurity was common and associated with impaired cognitive development	
						From 5 years: audiometry, AVLT, CMS, Tea-Ch, CBCL	No increased risk for cardiac or auditory morbidity	
VARIOUS (4 HL, 1 AL)	57	35	22 (children of women diagnosed with cancer who did not undergo chemo during pregnancy)	1997-2014	Premature birth was more prevalent in chemotherapy-exposed group (mean GA at birth: 36.7±2.5 weeks in exposed versus 38.2±2.7 in controls)	Bayley scale between 18 and 42 months of age	No difference in cognitive skills, academic achievement	Cardonick et al. [117]
						Wechsler test at 3-7 years of age	Higher rates of internalizing behavior problems in Bayley scale at 18, 36 months	
VARIOUS (2 ALL, 5 AML, 2 CML, 5 HL, 6 NHL)	132	97	132	INCIP database 2005-2018	Median GA (weeks) at birth 36.1 (27.4-40.7)		Median age 6.1 years	Vandenbroucke et al. [118]
					Prematurity rate: 60.6%	Wechsler test, CMS, CBCL, ANT, Cardiological assessment and echocardiography	No statistically significant between-group differences in the primary outcome full scale IQ, attention, or short-term memory	
					SGA = 14.9%		within normal ranges, statistically lower mean verbal IQ and visuospatial long-term memory in the study versus control group	
							Significantly higher values in diastolic blood pressure in chemotherapy-exposed and in a subgroup of 59 anthracycline-exposed	
							Study group 3x more likely to wear eye glasses	
							Hearing loss in 3 of 8 children exposed to cisplatin	

HEMATOLOGICAL MALIGNANCIES: 20 NHL, 16 HL, 9 AML, 7 CML, ALL 5	57	38	no	INCIP database 1991-2020	Median GA 36.4 (range 26.4-41.3) weeks	Bayley scale at 18, 36 months	No differences in general health, behavior and executive function.	Van Gerwen et al. [119]
					Median BW 2590 (720-4423) g	Wechsler scale at 6, 9, 12, 15 and 18 years	Normal cognitive outcome (median age for the last performed Bayley test: 1.7 years; median age for the last performed Wechsler test 10.7 years).	
					59.6% preterm infants (8.8% VP and 1.8% EP infants)	CMS	Scores were not related to duration of chemotherapy.	
						CBCL	Supportive care was associated with loss of the mother.	
HL	111	69	42 no-antenatal exposure	INCIP database 1969-2018	No differences in GA at birth, NICU admission and SGA between chemotherapy-exposed children and non-exposed	NA	NA	Maggen et al. [68]
					Lower birth weight percentiles in exposed neonates			
					Higher occurrence of obstetric complications in patients receiving chemotherapy: contractions and premature rupture of membranes			
NHL	75 (of whom 56 born to mother with DLBCL)	54 (of whom 46 born to mother with DLBCL)	no	INCIP database 1986-2019	SGA 39% (44.4% of infants born to mother with DLBCL)	NA	NA	Maggen et al. [36]
					No differences in preterm birth and birth weight percentiles between children prenatally exposed to cancer treatment and non-exposed.			
					Preterm birth 52%			
					Obstetric complications 41%			
					Neonatal complications 12.5%			

LEUKEMIA (38 AML, 42 ALL, 29 CML	108	56	no	INCIP data-base (1997-2020)	Stillbirth: 5% AML, 5% ALL, 0% CML. SGA: 48% ALL, 30% ML, 32% CML. Acute leuke-mia 48% with chemo vs 18% without chemo. Preterm birth: 69% ALL, 67% AML, 42% CML.	NA	NA	Maggen et al. [120]

Table 4 Early neonatal and long-term outcomes of infants born to mothers with hematologic cancer. *GA = Gestational Age; BW = Birth Weight; IQ = Intelligence Quotient, SGA = birth weight below the 10th perce*
ntile, , NICU = Neonatal Intensive Care Unit; AVLT = Auditory Verbal Learning Test; CMS = Children's Memory Scale; Tea-Ch = Test of Everyday Attention for Children; BRIEF = Behavior rating Inventory of Executive Function; CBCL = Child Behavior CheckList; ANT = Amsterdam Neuropsychological Tasks ; INCIP = International Network on Cancer, Infertility and Pregnancy

Looking at the most frequently occurring hematological cancers and their impact on pregnancy outcome:

- Acute leukemia: aggressive chemotherapy regimens are required with strong hematopoietic suppression (anemia, bleeding, and infection risks) and maternal side effects (nutrition, high physical and emotional stress) that affect the pregnancy. [116] Even without chemotherapy, higher rates of pregnancy terminations, growth restriction, miscarriage and intrauterine death are seen. Timely treatment of maternal acute leukemia results in improved maternal and fetal outcomes. [117,118]
- Lymphoma: obstetrical impact varies depending on the maternal organ involvement or compression but has an overall more favorable obstetric outcome.

Prenatal care for women with a hematological malignancy

<u>At diagnosis</u>

Accurate dating of the pregnancy is crucial for patient counseling on the maternal and fetal impact of diagnostic and therapeutic possibilities. A detailed structural scan is advised, both for medico-legal reasons and because it can influence patients' decision on further management. Non-invasive prenatal testing (NIPT) is often inconclusive because of the presence of cell-free tumor DNA. Cases have been published of patients with inconclusive NIPT due to the present of an asymptomatic lymphoma. [119] In case of an inconclusive NIPT, ultra-sonographic screening for markers for aneuploidy can be performed and invasive prenatal testing should be discussed. [120]

In case of a poor maternal prognosis before fetal viability when treatment cannot be safely delayed until the second trimester, patients should be offered termination of pregnancy. Induction chemotherapy is recommended before termination so the patient can better handle procedure related complications such as bleeding or infection.

Surveillance

Pregnant patients with cancer, especially those receiving chemotherapy, need additional ultrasound scans (q3-4weeks) to document adequate interval fetal growth. To evaluate fetal wellbeing, weekly non-stress testing via cardiotocography is advised from 34 weeks onwards, or at diagnosis of fetal growth restriction. In case of maternal complications (e.g. sepsis, pancytopenia, diffuse intravascular coagulation), additional fetal monitoring is required and obstetrical management should be adapted accordingly.

Cancer patients are at increased risk for preterm delivery, and standard treatment should be offered (steroids for lung maturation, tocolysis, $MgSO_4$ for fetal neuroprotection in cases of preterm labor prior to 32 weeks). [121] Iron deficiency should be screened for and supplemented. Anemia increases fetal IUGR/oligohydramnios, so transfusion cutoffs might be different for pregnant women compared to non-pregnant. When corticosteroids are part of the treatment regimen, patients are at increased risk for gestational diabetes so should have oral glucose tolerance test or glucose day profile monitoring. LMWH should be considered according to the RCOG guidelines. [122]

Gestational complications should be managed as in non-cancer patients and side effects of chemotherapy should be monitored as in non-pregnant patients.

Delivery planning

Delivery should be scheduled when the maternal clinical status is adequate to handle common labor complications (hemorrhage and infection) and the interval since the last chemotherapy administration is sufficient to ensure that chemotherapy has been eliminated from the fetus and hematological toxicity in mother and neonate is avoided. A three-week interval between last chemotherapy and delivery is recommended. Maternal platelets should be > 50 x10*9/L and neutrophils > 1000/µL at time of delivery. [115,123] Preferably, delivery should be planned at a minimum of 37 weeks of pregnancy.

Postpartum care

In all cases of cancer diagnosed during pregnancy, the placenta should be examined for metastases. Active malignant disease in the postpartum period is an indication for LMWH. [122] Live vaccines such as rubella to immunologically compromised postpartum women are contraindicated.

In general, agents with low molecular weight, high lipid-solubility and low protein binding are easily transferred to milk. Data on drug transfer through breastmilk are limited. [124] Chemotherapy metabolite levels were measured in the breast milk of three patients undergoing chemotherapy for 1-3 weeks after treatment. [125] For cyclophosphamide and carboplatin, discarding milk for 1-3 days can reduce relative infant dose (RID) to below 1% or 0.1%, allowing potential breastfeeding between cycles, while more study is needed to common on breastfeeding after receiving doxorubicin and cisplatin. For most chemotherapeutic drugs, oral bioavailability is low. Awaiting more *in vivo* and pharmacokinetic study data, we advise that breastfeeding can be considered from the time that the elimination period of at 5-7 half-lives for each chemotherapeutic agent has passed. For most agents, this occurs during the three-week interval recommended between chemotherapy during pregnancy (halt by 34 weeks) and delivery. After chemotherapy during pregnancy, a decreased breast milk supply is reported, which has been associated with an earlier gestational age at start of the treatment, and an increasing number of

cycles.[126] For nivolumab, cumulative RID over the first cycle was 9.8% in one patients and the measured concentration was even higher after administration of the second cycle.[127]

Infant's short and long-term outcomes

Neonates should be assessed by a neonatologist, and followed by a pediatrician for physical health, immune competence, potential cardiotoxicity and neurodevelopment. Available follow up studies conclude that when avoiding chemotherapy during organogenesis, and controlled for gestational age at birth, outcome of children born from pregnancies complicated by maternal cancer and treatment is comparable to the general population.[110,128-132]

Infants whose mothers received Rituximab in the 2nd/3rd trimester are born with B cell depletion with spontaneous resolution by 4-6 months without infectious complications. B-cell recovery is fast, showing a regular immunophenotype without loss of CD20 antigen, with no functional deficits and adequate vaccination IgG titers.[55,133-136]

Early neonatal and long-term outcomes of infants born to mothers with hematologic cancer are summarized in Table 4.

CONCLUSION

To optimize obstetrical and maternal outcomes, pregnant women with hematological cancers should receive standard treatment without delay whenever possible with an overarching goal of a full-term delivery, and should be followed in a multidisciplinary team including high-risk obstetric follow up. Enrollment of all cases of cancer diagnosed during pregnancy in the INCIP database is encouraged. Oncologists and obstetricians can seek advice about staging and treatment of cancer during pregnancy by contacting the advisory board ABCIP (https://www.ab-cip.org/).[137]

REFERENCES

1 An, Z.-Y. *et al.* Projected Global Trends in Hematological Malignancies: Incidence, Mortality, and Disability-Adjusted Life Years from 2020 to 2030. *Blood* **142**, 3810-3810 (2023).

2 de Haan, J. *et al.* Oncological management and obstetric and neonatal outcomes for women diagnosed with cancer during pregnancy: a 20-year international cohort study of 1170 patients. *The Lancet Oncology* **19**, 337-346 (2018).

3 Peccatori, F. A. *et al.* Cancer, pregnancy and fertility: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* **24 Suppl 6**, vi160-170 (2013).

4 Loibl, S. *et al.* Breast cancer diagnosed during pregnancy adapting recent advances in breast cancer care for pregnant patients. *JAMA Oncology* **1**, 1145-1153 (2015).

5 Amant, F. *et al.* Gynecologic cancers in pregnancy: Guidelines based on a third international consensus meeting. *Annals of Oncology* **30**, 1601-1612 (2019).

6 Lishner, M. *et al.* Hematologic malignancies in pregnancy: Management guidelines from an international consensus meeting. *Journal of Clinical Oncology* **34**, 501-508 (2016).

7 Milojkovic, D. & Apperley, J. F. How I treat leukemia during pregnancy. *Blood* **123**, 974-984 (2014).

8 Evens, A. M. *et al.* Lymphoma occurring during pregnancy: antenatal therapy, complications, and maternal survival in a multicenter analysis. *Journal of Clinical Oncology* **31**, 4132-4139 (2013).
9 Jha, P. *et al.* Imaging Cancer in Pregnancy. *Radiographics* **42**, 1494-1513 (2022).
10 Vandecaveye, V., Amant, F., Lecouvet, F., Van Calsteren, K. & Dresen, R. C. Imaging modalities in pregnant cancer patients. *International journal of gynecological cancer : official journal of the International Gynecological Cancer Society* **31**, 423-431 (2021).
11 Bourjeily, G. *et al.* Neonatal thyroid function: effect of a single exposure to iodinated contrast medium in utero. *Radiology* **256**, 744-750 (2010).
12 Adejolu, M., Shenoy-Bhangle, A. S. & McGettigan, M. Imaging modalities and optimized imaging protocols in pregnant patients with cancer. *Abdom Radiol (NY)* **48**, 1579-1589 (2023).
13 Han, S. N. *et al.* Feasibility of whole-body diffusion-weighted MRI for detection of primary tumour, nodal and distant metastases in women with cancer during pregnancy: a pilot study. *European Radiology* **28**, 1862-1874 (2017).
14 Westerland, O. *et al.* Comparison of the diagnostic performance and impact on management of 18F-FDG PET/CT and whole-body MRI in multiple myeloma. *Eur J Nucl Med Mol Imaging* **48**, 2558-2565 (2021).
15 Mayerhoefer, M. E. *et al.* Evaluation of diffusion-weighted MRI for pretherapeutic assessment and staging of lymphoma: results of a prospective study in 140 patients. *Clin Cancer Res* **20**, 2984-2993 (2014).
16 Tsuji, K. *et al.* Evaluation of staging and early response to chemotherapy with whole-body diffusion-weighted MRI in malignant lymphoma patients: A comparison with FDG-PET/CT. *J Magn Reson Imaging* **41**, 1601-1607 (2015).
17 Mayerhoefer, M. E. *et al.* Evaluation of Diffusion-Weighted Magnetic Resonance Imaging for Follow-up and Treatment Response Assessment of Lymphoma: Results of an 18F-FDG-PET/CT-Controlled Prospective Study in 64 Patients. *Clin Cancer Res* **21**, 2506-2513 (2015).
18 Begano, D., Söderberg, M. & Bolejko, A. TO USE OR NOT USE PATIENT SHIELDING ON PREGNANT WOMEN UNDERGOING CT PULMONARY ANGIOGRAPHY: A PHANTOM STUDY. *Radiat Prot Dosimetry* **189**, 458-465 (2020).
19 Van Calsteren, K. *et al.* Cancer during pregnancy: an analysis of 215 patients emphasizing the obstetrical and the neonatal outcomes. *Journal of Clinical Oncology* **28**, 683-689 (2010).
20 Garland, M. Pharmacology of drug transfer across the placenta. *Obstet Gynecol Clin North Am* **25**, 21-42 (1998).
21 Syme, M. R., Paxton, J. W. & Keelan, J. A. Drug transfer and metabolism by the human placenta. *Clin Pharmacokinet* **43**, 487-514 (2004).
22 van Gerwen, M. *et al.* Association of Chemotherapy Timing in Pregnancy With Congenital Malformation. *JAMA Netw Open* **4**, e2113180 (2021).
23 Cardonick, E. & Iacobucci, A. Use of chemotherapy during human pregnancy. *The Lancet. Oncology* **5**, 283-291 (2004).
24 Michalet, M. *et al.* Radiotherapy and pregnancy. *Cancer Radiother* **26**, 417-423 (2022).
25 Wong, Y. M. *et al.* A review on fetal dose in Radiotherapy: A historical to contemporary perspective. *Phys Med* **105**, 102513 (2023).
26 ICRP. Pregnancy and medical radiation. *Annals of the ICRP* **84**, 1-43 (2000).
27 Yoshimoto, Y., Kato, H. & Schull, W. J. Risk of cancer among children exposed in utero to A-bomb radiations, 1950-84. *Lancet* **2**, 665-669 (1988).
28 Van Assche, I. A. *et al.* Long-term neurocognitive, psychosocial, and physical outcomes after prenatal exposure to radiotherapy: a multicentre cohort study of the International Network on Cancer, Infertility, and Pregnancy. *The Lancet. Child & adolescent health* **8**, 433-442 (2024).
29 Heimovaara, J. H. *et al.* Proton therapy of a pregnant patient with nasopharyngeal carcinoma. *Clin Transl Radiat Oncol* **35**, 33-36 (2022).
30 La Tessa, C. *et al.* Out-of-field dose studies with an anthropomorphic phantom: comparison of X-rays and particle therapy treatments. *Radiother Oncol* **105**, 133-138 (2012).
31 Blommaert, J. *et al.* Challenges and opportunities for proton therapy during pregnancy. *Acta Obstet Gynecol Scand* **103**, 767-774 (2024).
32 Borgers, J. S. W. *et al.* Immunotherapy for cancer treatment during pregnancy. *The Lancet. Oncology* **22**, e550-e561 (2021).

33 Pentsuk, N. & van der Laan, J. W. An interspecies comparison of placental antibody transfer: new insights into developmental toxicity testing of monoclonal antibodies. *Birth defects research. Part B, Developmental and reproductive toxicology* **86**, 328-344 (2009).
34 *Comprehensive Cancer Information - National Cancer Institute*, https://www.cancer.gov (accessed Feb 21th 2024)
35 Lambertini, M., Peccatori, F. A. & Azim, H. A., Jr. Targeted agents for cancer treatment during pregnancy. *Cancer treatment reviews* **41**, 301-309 (2015).
36 Maggen, C. *et al.* Maternal and neonatal outcomes in 80 patients diagnosed with non-Hodgkin lymphoma during pregnancy: results from the International Network of Cancer, Infertility and Pregnancy. *Br J Haematol* **193**, 52-62 (2021).
37 Chelysheva, E. *et al.* Placental transfer of tyrosine kinase inhibitors used for chronic myeloid leukemia treatment. *Leuk Lymphoma* **59**, 733-738 (2018).
38 NTP Monograph: Developmental Effects and Pregnancy Outcomes Associated With Cancer Chemotherapy Use During Pregnancy. *NTP Monogr*, i-214 (2013).
39 Pye, S. M. *et al.* The effects of imatinib on pregnancy outcome. *Blood* **111**, 5505-5508 (2008).
40 Berveiller, P. *et al.* A dramatic fetal outcome following transplacental transfer of dasatinib. *Anticancer Drugs* **23**, 754-757 (2012).
41 Cortes, J. *et al.* Perspectives on Drug Development for the Treatment of Chronic Myeloid Leukemia in Pregnant Patients and Patients Who Are Breastfeeding. *Clinical cancer research : an official journal of the American Association for Cancer Research* (2024).
42 de Haan, J. *et al.* Severe Adverse Reaction to Vemurafenib in a Pregnant Woman with Metastatic Melanoma. *Case Rep Oncol* **11**, 119-124 (2018).
43 Baarslag, M. A. *et al.* Severe Immune-Related Enteritis after In Utero Exposure to Pembrolizumab. *N Engl J Med* **389**, 1790-1796 (2023).
44 Nolan, S., Czuzoj-Shulman, N. & Abenhaim, H. A. Obstetrical and newborn outcomes among women with acute leukemias in pregnancy: a population-based study. *J Matern Fetal Neonatal Med* **33**, 3514-3520 (2020).
45 Brenner, B., Avivi, I. & Lishner, M. Haematological cancers in pregnancy. *Lancet* **379**, 580-587 (2012).
46 Greenlund, L. J., Letendre, L. & Tefferi, A. Acute leukemia during pregnancy: a single institutional experience with 17 cases. *Leuk Lymphoma* **41**, 571-577 (2001).
47 Barnes, M. N., Barrett, J. C., Kimberlin, D. F. & Kilgore, L. C. Burkitt lymphoma in pregnancy. *Obstet Gynecol* **92**, 675-678 (1998).
48 Chelghoum, Y. *et al.* Acute leukemia during pregnancy: a report on 37 patients and a review of the literature. *Cancer* **104**, 110-117 (2005).
49 Stahl, M. *et al.* Management of hyperleukocytosis and impact of leukapheresis among patients with acute myeloid leukemia (AML) on short- and long-term clinical outcomes: a large, retrospective, multicenter, international study. *Leukemia* **34**, 3149-3160 (2020).
50 Bertoli, S. *et al.* Dexamethasone in hyperleukocytic acute myeloid leukemia. *Haematologica* **103**, 988-998 (2018).
51 Zhu, D., Tang, D., Chai, X., Zhang, G. & Wang, Y. Acute leukemia in pregnancy: a single institutional experience with 21 cases at 10 years and a review of the literature. *Ann Med* **53**, 567-575 (2021).
52 Hyoun, S. C., Običan, S. G. & Scialli, A. R. Teratogen update: methotrexate. *Birth Defects Res A Clin Mol Teratol* **94**, 187-207 (2012).
53 Horowitz, N. A. *et al.* Acute myeloid leukemia during pregnancy: a systematic review and meta-analysis. *Leuk Lymphoma* **59**, 610-616 (2018).
54 Sandley, M. & Angus, J. Asparaginase therapy in patients with acute lymphoblastic leukemia: expert opinion on use and toxicity management. *Leuk Lymphoma* **64**, 776-787 (2023).
55 Chakravarty, E. F., Murray, E. R., Kelman, A. & Farmer, P. Pregnancy outcomes after maternal exposure to rituximab. *Blood* **117**, 1499-1506 (2011).
56 Karagiannis, P. *et al.* Treatment of refractory acute myeloid leukaemia during pregnancy with venetoclax, high-dose cytarabine and mitoxantrone. *Br J Haematol* **192**, e60-e63 (2021).
57 Alrajhi, A. M. *et al.* The use of 5-azacytidine in pregnant patient with Acute Myeloid Leukemia (AML): a case report. *BMC pregnancy and childbirth* **19**, 394 (2019).
58 Mahdi, A. J. *et al.* Successful molecular targeted treatment of AML in pregnancy with Azacitidine and Sorafenib with no adverse fetal outcomes. *Br J Haematol* **180**, 603-604 (2018).

59 Sanz, M. A. *et al.* Management of acute promyelocytic leukemia: recommendations from an expert panel on behalf of the European LeukemiaNet. *Blood* **113**, 1875-1891 (2009).
60 Sanz, M. A. *et al.* Management of acute promyelocytic leukemia: updated recommendations from an expert panel of the European LeukemiaNet. *Blood* **133**, 1630-1643 (2019).
61 Santolaria, A., Perales, A., Montesinos, P. & Sanz, M. A. Acute Promyelocytic Leukemia during Pregnancy: A Systematic Review of the Literature. *Cancers (Basel)* **12** (2020).
62 Bachanova, V. & Connors, J. M. Hodgkin lymphoma in pregnancy. *Curr Hematol Malig Rep* **8**, 211-217 (2013).
63 Pinnix, C. C. *et al.* Maternal and Fetal Outcomes After Therapy for Hodgkin or Non-Hodgkin Lymphoma Diagnosed During Pregnancy. *JAMA Oncol* **2**, 1065-1069 (2016).
64 Pereg, D., Koren, G. & Lishner, M. The treatment of Hodgkin's and non-Hodgkin's lymphoma in pregnancy. *Haematologica* **92**, 1230-1237 (2007).
65 Lavi, N., Horowitz, N. A. & Brenner, B. An update on the management of hematologic malignancies in pregnancy. *Womens Health (Lond)* **10**, 255-266 (2014).
66 Odelia, A. *et al.* Continuing dilemmas in the management of lymphoma during pregnancy: review of a 10-point case-based questionnaire. *International Journal of Clinical Oncology* **22**, 190-199 (2017).
67 Eyre, T. A., Lau, I. J., Mackillop, L. & Collins, G. P. Management and controversies of classical Hodgkin lymphoma in pregnancy. *Br J Haematol* **169**, 613-630 (2015).
68 Maggen, C. *et al.* Obstetric and maternal outcomes in patients diagnosed with Hodgkin lymphoma during pregnancy: a multicentre, retrospective, cohort study. *The Lancet Haematology* **6**, e551-e561 (2019).
69 *ADCETRIS. EMA Product Information. https://www.ema.europa.eu/en/documents/product-information/adcetris-epar-product-information_en.pdf. [accessed on 2024-08-09]*.
70 Hay, A. E. *et al.* An individual patient-data comparison of combined modality therapy and ABVD alone for patients with limited-stage Hodgkin lymphoma. *Ann Oncol* **24**, 3065-3069 (2013).
71 Evens, A. M. *et al.* Checkpoint inhibitor immunotherapy during pregnancy for relapsed-refractory Hodgkin lymphoma. *Am J Hematol* (2022).
72 Mazonakis, M., Varveris, H., Fasoulaki, M. & Damilakis, J. Radiotherapy of Hodgkin's disease in early pregnancy: embryo dose measurements. *Radiother Oncol* **66**, 333-339 (2003).
73 Woussen, S. *et al.* Clinical indications and radiation doses to the conceptus associated with CT imaging in pregnancy: a retrospective study. *Eur Radiol* **26**, 979-985 (2016).
74 Farooq, F. *et al.* An international real-world analysis of relapsed/refractory lymphoma occurring during pregnancy. *Blood Adv* **7**, 5480-5484 (2023).
75 Evens, A. M. *et al.* Lymphoma occurring during pregnancy: antenatal therapy, complications, and maternal survival in a multicenter analysis. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology* **31**, 4132-4139 (2013).
76 Van Calsteren, K. *et al.* Cancer during pregnancy: An analysis of 215 patients emphasizing the obstetrical and the Neonatal outcomes. *Journal of Clinical Oncology* **28**, 683-689 (2010).
77 Dunleavy, K. & McLintock, C. How I treat lymphoma in pregnancy. *Blood* **136**, 2118-2124 (2020).
78 Lishner, M., Zemlickis, D., Sutcliffe, S. B. & Korent, G. Non-hodgkin's lymphoma and pregnancy. *Leukemia and Lymphoma* (1994).
79 Di Ciaccio, P. R. *et al.* The clinical features, management and outcomes of lymphoma in pregnancy: A multicentre study by the Australasian Lymphoma Alliance. *Br J Haematol* **201**, 887-896 (2023).
80 Tilly, H. *et al.* Polatuzumab Vedotin in Previously Untreated Diffuse Large B-Cell Lymphoma. *N Engl J Med* **386**, 351-363 (2022).
81 Lam, M. S. Treatment of Burkitt's lymphoma during pregnancy. *Ann Pharmacother* **40**, 2048-2052 (2006).
82 Peterson, C., Lester, D. R., Jr. & Sanger, W. Burkitt's lymphoma in early pregnancy. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology* **28**, e136-138 (2010).
83 Chamuleau, M. E. D. *et al.* R-CODOX-M/R-IVAC versus DA-EPOCH-R in patients with newly diagnosed Burkitt lymphoma (HOVON/SAKK): final results of a multicentre, phase 3, open-label, randomised trial. *Lancet Haematol* **10**, e966-e975 (2023).
84 Godfrey, A. L., Green, A. C. & Harrison, C. N. Essential thrombocythemia: challenges in clinical practice and future prospects. *Blood* **141**, 1943-1953 (2023).
85 Alimam, S. *et al.* Pregnancy outcomes in myeloproliferative neoplasms: UK prospective cohort study. *Br J Haematol* **175**, 31-36 (2016).

86 Gangat, N. *et al.* Pregnancy outcomes in myeloproliferative neoplasms: A Mayo Clinic report on 102 pregnancies. *Am J Hematol* **95**, E114-e117 (2020).
87 Landtblom, A. R. *et al.* Pregnancy and childbirth outcomes in women with myeloproliferative neoplasms-a nationwide population-based study of 342 pregnancies in Sweden. *Leukemia* **36**, 2461-2467 (2022).
88 Wille, K. *et al.* Outcome of 129 Pregnancies in Polycythemia Vera Patients: A Report of the European LeukemiaNET. *Hemasphere* **7**, e882 (2023).
89 Maze, D. *et al.* Association of Treatments for Myeloproliferative Neoplasms During Pregnancy With Birth Rates and Maternal Outcomes: A Systematic Review and Meta-analysis. *JAMA Netw Open* **2**, e1912666 (2019).
90 Robinson, S. E. & Harrison, C. N. How we manage Philadelphia-negative myeloproliferative neoplasms in pregnancy. *Br J Haematol* **189**, 625-634 (2020).
91 Gangat, N. & Tefferi, A. Myeloproliferative neoplasms and pregnancy: Overview and practice recommendations. *Am J Hematol* **96**, 354-366 (2021).
92 Skeith, L., Carrier, M., Robinson, S. E., Alimam, S. & Rodger, M. A. Risk of venous thromboembolism in pregnant women with essential thrombocythemia: a systematic review and meta-analysis. *Blood* **129**, 934-939 (2017).
93 Abruzzese, E. *et al.* Chronic Myeloid Leukemia and Pregnancy: When Dreams Meet Reality. State of the Art, Management and Outcome of 41 Cases, Nilotinib Placental Transfer. *J Clin Med* **11** (2022).
94 Chelysheva, E. *et al.* Chronic myeloid leukemia diagnosed in pregnancy: management and outcome of 87 patients reported to the European LeukemiaNet international registry. *Leukemia* **38**, 788-795 (2024).
95 Kulasekararaj, A. *et al.* Guidelines for the diagnosis and management of adult aplastic anaemia: A British Society for Haematology Guideline. *Br J Haematol* **204**, 784-804 (2024).
96 Rottenstreich, A. & Bussel, J. B. Treatment of immune thrombocytopenia during pregnancy with thrombopoietin receptor agonists. *Br J Haematol* **203**, 872-885 (2023).
97 Michel, M. *et al.* Use of thrombopoietin receptor agonists for immune thrombocytopenia in pregnancy: results from a multicenter study. *Blood* **136**, 3056-3061 (2020).
98 Bussel, J. B. & Knightly, K. A. Immune thrombocytopenia (ITP) in pregnancy. *Br J Haematol* **204**, 1176-1177 (2024).
99 Paziana, K. *et al.* Ciclosporin use during pregnancy. *Drug Saf* **36**, 279-294 (2013).
100 Tichelli, A. *et al.* Outcome of pregnancy and disease course among women with aplastic anemia treated with immunosuppression. *Ann Intern Med* **137**, 164-172 (2002).
101 Kelly, R. J. *et al.* Eculizumab in Pregnant Patients with Paroxysmal Nocturnal Hemoglobinuria. *N Engl J Med* **373**, 1032-1039 (2015).
102 Mahmoud, H. K., Samra, M. A. & Fathy, G. M. Hematologic malignancies during pregnancy: A review. *J Adv Res* **7**, 589-596 (2016).
103 Rizack, T., Mega, A., Legare, R. & Castillo, J. Management of hematological malignancies during pregnancy. *Am J Hematol* **84**, 830-841 (2009).
104 Magen, H., Simchen, M. J., Erman, S. & Avigdor, A. Diagnosis and management of multiple myeloma during pregnancy: case report, review of the literature, and an update on current treatments. *Ther Adv Hematol* **13**, 20406207211066173 (2022).
105 Cabañas-Perianes, V. *et al.* 'Management multiple myeloma during pregnancy: a case report and review'. *Hematol Oncol* **34**, 108-114 (2016).
106 Green, S. B. & Pappas, A. L. Effects of maternal bisphosphonate use on fetal and neonatal outcomes. *Am J Health Syst Pharm* **71**, 2029-2036 (2014).
107 Smith, D. *et al.* Myeloma presenting during pregnancy. *Hematol Oncol* **32**, 52-55 (2014).
108 Kasenda, B. *et al.* Management of multiple myeloma in pregnancy: strategies for a rare challenge. *Clin Lymphoma Myeloma Leuk* **11**, 190-197 (2011).
109 Dimopoulos, M. A. *et al.* Multiple myeloma: EHA-ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up(†). *Ann Oncol* **32**, 309-322 (2021).
110 Nulman, I. *et al.* Neurodevelopment of children exposed in utero to treatment of maternal malignancy. *Br J Cancer* **85**, 1611-1618 (2001).
111 Smith, C., Teng, F., Branch, E., Chu, S. & Joseph, K. S. Maternal and Perinatal Morbidity and Mortality Associated With Anemia in Pregnancy. *Obstet Gynecol* **134**, 1234-1244 (2019).

112 Rubrecht, A. E., Seifert, R. P. & Shenoy, A. Maternal Hematologic Neoplasms during Pregnancy: Histologic Findings in the Placenta. *Placenta* **104**, 195-198 (2021).
113 Wolters, V. *et al.* Placental pathology in cancer during pregnancy and after cancer treatment exposure. *Placenta* **111**, 33-46 (2021).
114 Glanc, P. Fetal and placental metastases associated with maternal cancers. *Abdom Radiol (NY)* **48**, 1784-1792 (2023).
115 La Nasa, M., Gaughan, J. & Cardonick, E. Incidence of Neonatal Neutropenia and Leukopenia After In Utero Exposure to Chemotherapy for Maternal Cancer. *Am J Clin Oncol* **42**, 351-354 (2019).
116 Van Assche, I. A., Lemiere, J., Amant, F. & Van Calsteren, K. Direct and indirect effects on child neurocognitive development when maternal cancer is diagnosed during pregnancy: What do we know so far? *Critical reviews in oncology/hematology* **179**, 103824 (2022).
117 Catanzarite, V. A. & Ferguson, J. E. Acute leukemia and pregnancy: a review of management and outcome, 1972-1982. *Obstet Gynecol Surv* **39**, 663-678 (1984).
118 Hauenstein, E., Seidl, S., Schneider, K. T. & Fischer, T. Stillbirth in week 19 of pregnancy followed by maternal death as a consequence of refused chemotherapy for non-hodgkin's lymphoma--significance of adjuvant chemotherapy in women of reproductive age. *Onkologie* **33**, 692-694 (2010).
119 Amant, F. *et al.* Presymptomatic Identification of Cancers in Pregnant Women During Noninvasive Prenatal Testing. *JAMA Oncol* **1**, 814-819 (2015).
120 Lenaerts, L., Van Calsteren, K., Che, H., Vermeesch, J. R. & Amant, F. Pregnant women with confirmed neoplasms should not have noninvasive prenatal testing. *Prenatal diagnosis* **39**, 1162-1165 (2019).
121 Wolf, H. T. *et al.* Magnesium sulphate for fetal neuroprotection at imminent risk for preterm delivery: a systematic review with meta-analysis and trial sequential analysis. *Bjog* **127**, 1180-1188 (2020).
122 *Green-top guideline no. 37: reducing the risk of thrombosis and embolism during pregnancy and the puerperium. London: RCOG; 2009*, https://www.rcog.org.uk/media/m4mbpjwi/gtg-no37a-2015_amended-2023.pdf (accessed Aug 9th 2024)
123 Reynoso, E. E. *et al.* Acute leukemia during pregnancy: The Toronto Leukemia Study Group Experience with long-term follow-up of children exposed in utero to chemotherapeutic agents. *Journal of Clinical Oncology* (1987).
124 Codacci-Pisanelli, G. *et al.* Breastfeeding during R-CHOP chemotherapy: please abstain! *Eur J Cancer* **119**, 107-111 (2019).
125 Damoiseaux, D. *et al.* Presence of Five Chemotherapeutic Drugs in Breast Milk as a Guide for the Safe Use of Chemotherapy During Breastfeeding: Results From a Case Series. *Clin Pharmacol Ther* **112**, 404-410 (2022).
126 Stopenski, S., Aslam, A., Zhang, X. & Cardonick, E. After Chemotherapy Treatment for Maternal Cancer During Pregnancy, Is Breastfeeding Possible? *Breastfeed Med* **12**, 91-97 (2017).
127 de Jong, K. *et al.* High accumulation of nivolumab in human breast milk: A case report. *Biomed Pharmacother* **166**, 115354 (2023).
128 Amant, F. *et al.* Long-term cognitive and cardiac outcomes after prenatal exposure to chemotherapy in children aged 18 months or older: An observational study. *The Lancet Oncology* **13**, 256-264 (2012).
129 Amant, F. *et al.* Pediatric outcome after maternal cancer diagnosed during pregnancy. *New England Journal of Medicine* **373**, 1824-1834 (2015).
130 van Gerwen, M. *et al.* Long-term neurodevelopmental outcome after prenatal exposure to maternal hematological malignancies with or without cytotoxic treatment. *Child Neuropsychol* **27**, 822-833 (2021).
131 Cardonick, E. H., Gringlas, M. B., Hunter, K. & Greenspan, J. Development of children born to mothers with cancer during pregnancy: Comparing in utero chemotherapy-exposed children with nonexposed controls. *American Journal of Obstetrics and Gynecology* (2015).
132 Vandenbroucke, T. *et al.* Child development at 6 years after maternal cancer diagnosis and treatment during pregnancy. *Submitted* (2020).
133 Decker, M., Rothermundt, C., Holländer, G., Tichelli, A. & Rochlitz, C. Rituximab plus CHOP for treatment of diffuse large B-cell lymphoma during second trimester of pregnancy. *The Lancet. Oncology* **7**, 693-694 (2006).
134 Klink, D. T., van Elburg, R. M., Schreurs, M. W. & van Well, G. T. Rituximab administration in third trimester of pregnancy suppresses neonatal B-cell development. *Clin Dev Immunol* **2008**, 271363 (2008).

135 Rey, J. *et al.* Rituximab combined with chemotherapy for lymphoma during pregnancy. *Leuk Res* **33**, e8-9 (2009).
136 Friedrichs, B. *et al.* The effects of rituximab treatment during pregnancy on a neonate. *Haematologica* **91**, 1426-1427 (2006).
137 Amant, F., Heimovaara, J. H., Lok, C. A. R. & Van Calsteren, K. The Advisory Board on Cancer, Infertility and Pregnancy: a virtual on-demand multidisciplinary tumour board. *The Lancet Oncology* (2022).

Chapter 10 Immunotherapy for cancer treatment during pregnancy

Jessica Borgers[*], **Joosje Heimovaara[*],** Elyce Cardonick, Daan Dierickx, Matteo Lambertini, John Haanen, Frédéric Amant

The Lancet Oncology, December 2021
[*] Contributed equally to the manuscript

ABSTRACT

Immunotherapy has greatly improved outcomes for subgroups of patients with cancer. As indications keep expanding, there is an unmet need to gain a better understanding of the effect of these therapies on pregnancy and fertility. During pregnancy, substantial adaptations occur in the maternal immune system to maintain protection against pathogens while avoiding detrimental reactions to the semi-allogeneic fetus. The pathways involved in the establishment of this fetomaternal tolerance can be hijacked by cancers. Immunotherapies that target these inhibitory pathways, or that directly interact with the regulatory immune cells involved in tolerance mechanisms, might therefore result in complications during pregnancy. Similarly, by activating the patient's immune system with immunotherapy, a broad range of immune-related adverse events can occur that could negatively affect the fetus or impede a future desired pregnancy. This Review summarises preclinical and clinical data related to the use of immunotherapy during pregnancy, including all approved immune checkpoint inhibitors, recombinant cytokines, cell therapies, vaccines, and immunomodulatory drugs.

INTRODUCTION

During the past two decades, oncological treatment options have increased substantially, leading to improved outcomes for patients with cancer. Cancer during pregnancy is uncommon, occurring at a rate of about 140 per 100,000 pregnancies.[1] However, this incidence is increasing, both because women now tend to postpone childbirth to a later age and because non-invasive prenatal tests are able to detect early cancers during pregnancy.[2,3] Oncological treatment for pregnant patients should follow standard guidelines as much as possible. Surgical treatment during pregnancy is possible in most cases, regardless of gestational age. Radiotherapy should be planned carefully because the impact of radiation on the fetus depends on gestational age, radiation field, and radiation dose.[4] Because most chemotherapeutics can easily cross the placenta, these should not be administered before the 12th week of gestation to avoid the risk of congenital malformations.[5,6] The sparse data available on targeted and hormonal therapies have shown that most agents are contraindicated and should be postponed until after delivery, except for rituximab and imatinib, which can be administered after the first trimester.[7] In the past 10 years, immunotherapies—including immune check- point inhibitors (ICIs), oncolytic viruses, and adoptive cell therapies—have become available for many cancer types, but still very few preclinical and clinical data are available on how these immunotherapies might affect pregnancy, the fetus, and fertility.

The immune system has a vital role in protecting the host against pathogens, while maintaining self-tolerance.[8] Cancer cells developing from normal cells might be detectable by the immune system, but often hijack tolerance mechanisms to evade attack.[9] This immune escape is crucial for the development, outgrowth, invasion, and metastatic ability of malignant cells. Cancer immunotherapy aims to restore the balance by activating patients' immune systems to overcome adaptive resistance and eradicate the tumour cells. However, overcoming self-tolerance, especially by targeting immune checkpoints, has led to a broad range of immune-related adverse events,[10] and might be particularly important during pregnancy because, as the maternal immune system needs to develop tolerance to the semi-allogeneic fetus.[11] Treatment with immuno- therapy could disrupt or prevent the establishment of fetomaternal tolerance, with consequences for both mother and child. Furthermore, little is known about the direct effects of these drugs, cytokines, or adoptive cell therapies on the fetus. As indications for immunotherapy expand and this treatment is used more frequently in both curative and palliative settings, the need to understand the effects of immunotherapy during pregnancy and on fertility is increasing. In this Review, we aim to provide an overview of immunological changes during gestation and of the available preclinical and clinical data regarding the use of approved immunotherapies during pregnancy and their potential impact on future conception.

THE IMMUNE SYSTEM DURING PREGNANCY

The maternal immune system is in a modulated state during pregnancy and develops tolerance to the semi-allogeneic fetus, which expresses both maternal and paternal antigens, while maintaining the ability to protect against infections and toxins. [11] T This development is characterised by three distinct immunological phases: firstly, a pro-inflammatory state throughout early pregnancy is essential for implantation and placentation in the uterus; [12] secondly, in the second and third trimesters, cell populations create an anti-inflammatory environment in the uterus; [13] and finally, the last phase is associated with parturition, in which a second pro-inflammatory stage is initiated to promote uterine contraction, delivery, and expulsion of the placenta. [13,14]

Fetomaternal tolerance

The uterine decidua (the maternal–fetal interface) has a crucial role in immunological protection and production of the different hormones, enzymes, and cytokines necessary for a successful pregnancy. [15] It consists of trophoblasts, decidual stromal cells, and immune cells (natural killer cells, macrophages, and lymphocytes; figure 1). [16] Interactions between these cells are key for the regulation of trophoblast invasion, placental development, and fetomaternal tolerance. [15]

Natural killer cells are the most prevalent in the first trimester and they account for 70% of decidual immune cells. [17] They are thought to have a key role in the tolerance of normal trophoblasts and to promote uterine vascular change. [17] Trophoblasts express both maternal and paternal antigens and help to sustain fetal development. [18,19] With no MHC expression (including HLA-A, HLA-B, and most MHC class II antigens) on their surface, trophoblasts evade recognition by the maternal immune system (eg, by preventing T-cell activation). [20,21] Extravillous trophoblasts do express HLA-C, HLA-E, and HLA-G, which improves maternal immune tolerance and helps them to escape recognition by natural killer cells. [21]

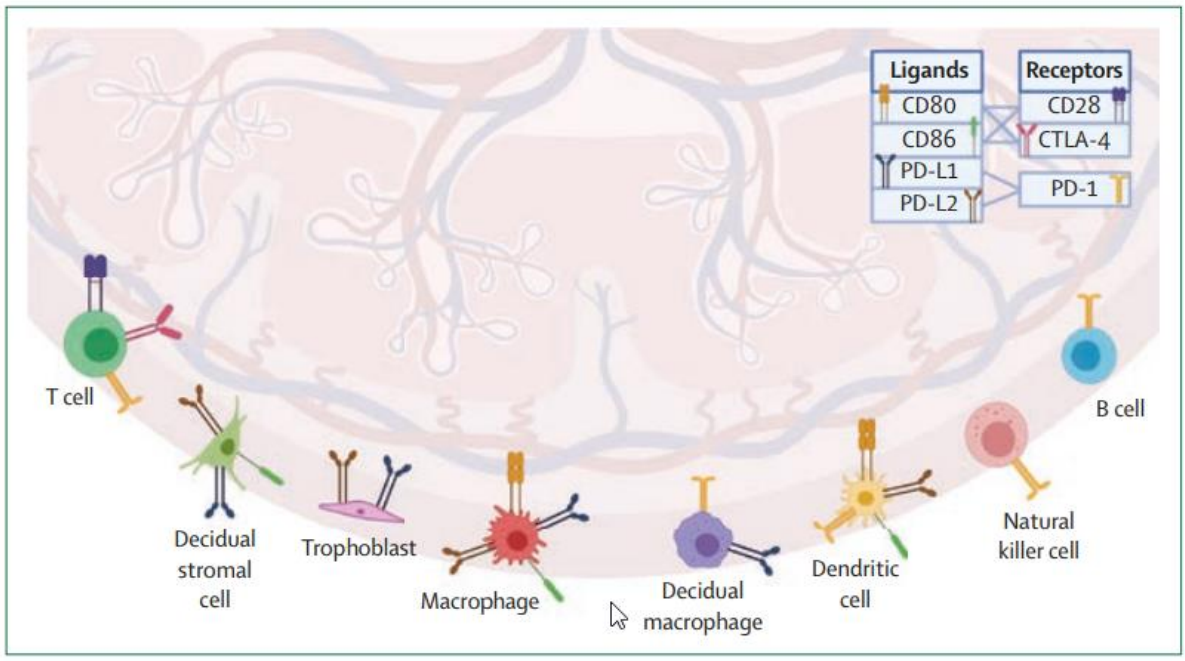


Figure 1. Relevant receptors on decidual immune cells. *An overview of the decidual immune cells and their expressed receptors of importance for fetomaternal tolerance.*

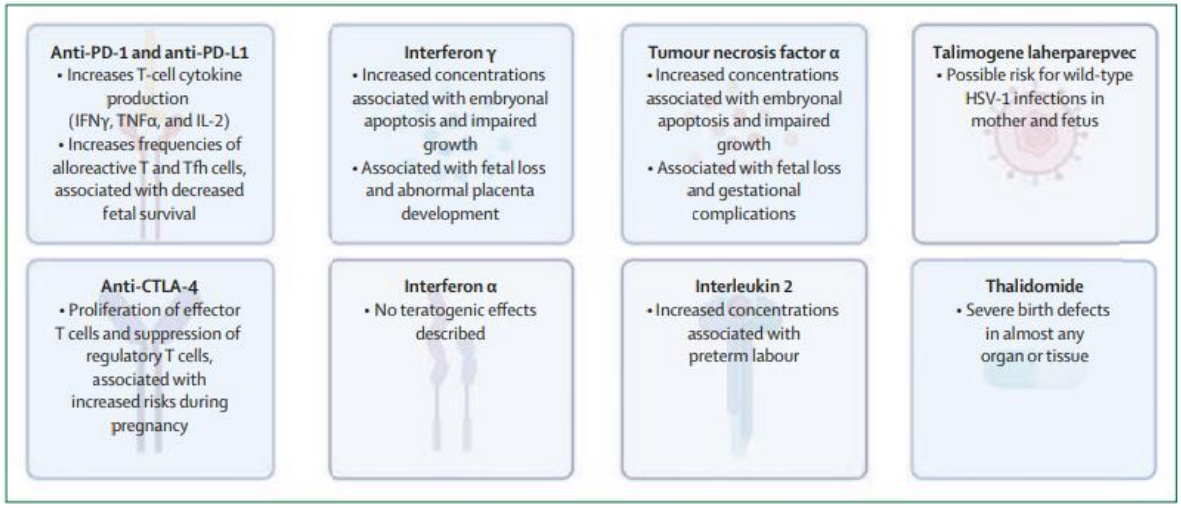


Figure 2. Adverse effects of the activity of targetable pathways or cytokines during pregnancy. *Each square represents a receptor, cytokine, or drug that can be used or targeted in cancer treatment, showing their role during pregnancy or fetal development. HSV-1=herpes simplex virus type 1. Tfh cell=T follicular helper cell.*

PD-1 and its ligands, PD-L1 and PD-L2, form co- inhibitory pathways that regulate the balance between T-cell activation, peripheral tolerance, and immune- mediated tissue damage, which are all crucial to establishing fetomaternal tolerance and maintaining pregnancy. [22] Interactions between decidual stromal cells and CD4+ T cells, via the PD-1–PD-L1 pathway, reduce the production of pro-inflammatory

cytokines and establish an immunosuppressive state at the maternal–fetal interface that favours implantation.[22,23] PD-1 is primarily expressed by lymphocytes (figure 1). Its expression decreases on peripheral T cells during the first trimester and increases on decidual immune cell subpopulations, on which it remains elevated throughout pregnancy.[24] PD-1 regulates T-cell homeostasis and has an important role in peripheral tolerance and prevention of autoimmunity.[25] PD-L1 is expressed by trophoblasts, decidual macrophages, and decidual stromal cells, and its expression increases substantially from 10–12 weeks of gestation onwards.[23,26] PD-L1 expression on decidual stromal cells reduces T-cell production of cytokines (eg, interferon γ [IFNγ], tumour necrosis factor α [TNFα], and interleukin 2 [IL-2]). Dysfunction of the PD-1–PD-L1 pathway and the resulting insufficient T-cell inhibition can lead to adverse pregnancy outcomes.[27] In early pregnancy, the expression of PD-L1 and MHC molecules by decidual macrophages enables them to suppress secretion of IFNγ by activated T cells, which is essential to establish and maintain maternal–fetal tolerance.[28,29] IFNγ production subsides in the second and third trimesters.[30] High IFNγ concentrations induce gestational complications (eg, fetal loss; figure 2) in animal studies,[31] probably caused by an immune-mediated decline of endometrial neovasculature in the early post- implantation period, which results in fetal stress.[29]

Another important inhibitory immune signalling pathway is that of CTLA-4 and its ligands CD80 and CD86. CTLA-4 is predominantly expressed on regulatory T cells (Tregs) in the decidua (figure 1), and contributes to the induction of peripheral tolerance and Treg-mediated suppression in mice.[32] Tregs are recruited before implantation to prime the immune-microenvironment in the uterus.[33] The expression of CTLA-4 on the decidua probably remains unchanged throughout pregnancy, possibly due to the low expression rate by decidual Tregs, although some studies report minimal decidual CTLA-4 expression.[34,35] CTLA-4 expression has immunosuppressive effects at the fetomaternal interface, because it correlates positively with anti-inflammatory cytokine secretion and negatively with pro-inflammatory cytokine secretion (figure 2).[36,37] CD80 and CD86 are costimulatory signals for decidual stromal cells and assist decidual dendritic cells in maintaining a Th2-dominant state, which is correlated with beneficial gestational outcomes.[38] Moreover, ligation of CD80 and CD86 with CTLA-4-positive decidual Tregs induces expression of indoleamine 2,3-dioxygenase, which promotes fetomaternal tolerance, especially during early pregnancy.[39]

Systemic immune regulation during pregnancy

T cells are the most important adaptive immune cells in the decidua, and a balance between T helper (Th) 1, Th2 and Th17 cells, and Tregs is associated with normal pregnancy.[40] Th1 cells produce IL-2 and IFNγ and are involved in cellular immunity. Th2 cells produce IL-4, IL-6 and IL-10 and are involved in

humoral immunity. Th17 cells produce IL-17 and play important roles in the induction of inflammation. [39,41] An imbalance between these signalling molecules might underlie the pathophysiology of pre-eclampsia, preterm labour and spontaneous abortion. [40] During pregnancy, a shift from cell-mediated (Th1-dominant) to humoral (Th2-dominant) response appears to takes place. [42] Th1-dominant and Th17-dominant diseases, such as rheumatoid arthritis, multiple sclerosis, and Graves' disease, show improvement during pregnancy, whereas worsening of Th2-dominant diseases, such as systemic lupus erythematosus and systemic sclerosis have been observed during gestation. [43] However, spontaneous abortion has been reported both with predominant Th1-type and Th2-dominant immunity. [44]
Furthermore, secretion of cytokines (Th1-type and Th2-type), seems to be upregulated in preterm labour (figure 2). Decreased IL-2 level concentrations have been suggested to help maintaining the fetal allograft. [45] IL-2 induces secretion of IFNγ, IL-4 and TNFα, which have been shown to be embryotoxic by inducing apoptosis and impairing growth. [46]

IMMUNE CHECKPOINT INHIBITORS

By blocking the immune checkpoints CTLA-4, PD-1, and PD-L1, ICIs have the ability to re-activate restrained T cell mediated antitumour responses, which has resulted in better survival rates for many cancer types. The antitumour responses are often durable and have relatively favourable toxicity profiles. [10] Here, we discuss current knowledge about the use of ICIs and the potential risks of immune-related adverse events during pregnancy.

Preclinical data

Anti-PD-1 and anti-PD-L1

The PD-1-PD-L1 pathway is thought to have an essential role in maintaining fetal tolerance. Treatment with anti-PD-1 and anti-PD-L1 monoclonal antibodies could be problematic during pregnancy: by blocking the interaction between PD-1 and PD-L1, ICIs enhance the functional activity of T cells towards tumour cells, but simultaneously abrogate the established fetomaternal immunotolerance. [27] This outcome could lead to adverse effects on the pregnancy, as shown in several animal models and case reports (table 1).

Guleria and colleagues[19] showed that pharmacological blocking or induction of a genetic deficiency in the PD-1–PD-L1 pathway increases the risk of spontaneous resorption and reduces litter sizes of allogeneic, but not syngeneic, conceptuses in mouse models. PD-L1 expression on the placenta of these syngeneic conceptuses was negligible, whereas it could be detected as early as 10 days after conception on the placenta of allogeneic conceptuses, indicating the importance of the PD-1–PD-L1

pathway as a negative regulator of maternal alloimmune T-cell responses against the fetus. [19] Furthermore, it has been shown that both blockage and deficiency of PD-L1 results in suppression of $CD4^{+}CD25^{+}$ Tregs, and increased frequencies of alloreactive T vells and T follicular helper cells at the uteroplacental interface, which are all associated with decreased fetal survival rates (figure 2). [47,48] The importance of Tregs in fetal protection is further supported by the results of the work by Habicht and colleagues[49], who showed that mice depleted of Tregs have increased fetal resorption rates, and that transfer of Tregs from normal pregnant mice to abortion-prone mice significantly improved fetal survival rates. This effect was reversed when these mice were treated with anti-PD-L1 monoclonal antibodies. [49] Non-human primate studies in cynomolgus monkeys have shown that treatment with 10mg/kg or more of the anti-PD-1 agent nivolumab twice weekly (9- 42 times higher than the clinical dose of 3 mg/kg), resulted in an increased risk of fetal growth restriction, premature delivery, and embryonal, fetal, and neonatal death compared with placebo. [50] Pembrolizumab was never tested in non-human primate studies, but on the basis of their similar mechanism of action, the assumed risk of reproductive toxic effects is believed to be similar. Importantly, despite the increased risk of pregnancy loss in animal models exposed to anti-PD-L1, no increased risk of malformations, immunological deficiencies, or neurological complications in surviving offspring is apparent. [19,49]

Anti-CTLA-4

The role of the CTLA-4 axis in fetomaternal tolerance is less clear than the PD-1-PD-L1 axis. By competing with CD28 for binding to CD80 and CD86 molecules, treatment with anti-CTLA-4 results in the expansion of effector T cells and Tregs in lymph nodes and in the accumulation of tumour-infiltrating effector T cells, while selectively depleting CTLA-4^{high} Tregs. [51,52] As a result of alterations in T cell response early on at sites of T cell activation, such as in lymphoid tissues, rather than exclusively in peripheral tissue, treatment with anti-CTLA-4 leads to a more general state of immune activation than treatment with anti-PD-1 monoclonal antibodies does. [50,51,53] However, as CTLA-4 signalling inhibits T cell activation, blockage of this negative costimulatory checkpoint leads to the proliferation and activation of effector T cells and suppression of Tregs, which are important in protecting the fetus from rejection by maternal immune cells (figure 2). [37,39,48,51] Therefore, blocking CTLA-4 is probably associated with increased risks during pregnancy.

An important role of CTLA-4 in pregnancy outcomes was first evidenced in a mouse study done by Miwa and colleagues, in 2005. [54] Later, Li and colleagues[55] showed that adenovirus-mediated CTLA4Ig (a protein resulting from the fusion of the extracellular domain of CTLA-4 and IgG1 and a competitive inhibitor of the B7- mediated and CD28-mediated costimulatory pathway) gene transfer was able to expand peripheral CD4+CD25+ Tregs and improve pregnancy outcomes in an abortion-prone mouse

model. Similarly, extensive CTLA4Ig expression at the uteroplacental interface suggests that CTLA4Ig is important in maintaining fetomaternal tolerance.[55] These data were further supported by results of a reproductive toxicity test in cynomolgus monkeys, which showed that administration of ipilimumab at concentrations of 2·6–7·2 times the clinical dose of 3 mg/kg did not induce treatment-related adverse events within the first two trimesters.[56,57] However, in the third trimester, a dose-related decrease in maternal weight and increased incidence of stillbirth, premature delivery, and infant mortality were observed.[56,57] In addition, Wang and colleagues[58] showed that blocking CTLA-4 or HAVcr-2 (another immune checkpoint currently being explored in clinical trials [eg, NCT03680508, NCT03961971, NCT04139902]), or both, led to increased embryo resorption rates, decreased fetal growth, and reduction of litter sizes. These events were associated with altered frequency and cytokine profiles of decidual CD4+ T cells, which are important in maintaining tolerance to the semi-allogeneic fetus.[58]

Clinical data

Seven ICIs are currently available as standard-of-care treatment: three anti-PD-1 monoclonal antibodies (pembrolizumab, nivolumab, and cemiplimab), three anti-PD-L1 monoclonal antibodies (atezolizumab, avelumab, and durvalumab), and one anti-CTLA-4 monoclonal antibody (ipilimumab); more are in clinical development.[59]

To date, there are seven published case reports of women who either conceived while on ICI-treatment (n = 5) or initiated treatment during pregnancy (n = 2, initiated at week 9 or at week 18), including two twin pregnancies (figure 3, appendix 1).[60-66] Six patients were diagnosed with metastatic melanoma, one patient with a stage I placental site trophoblastic tumour who declined hysterectomy and received pembrolizumab as primary systemic treatment. Of the patients with melanoma, two women received nivolumab as monotherapy[63,65], three received nivolumab in combination with ipilimumab[60,61,64], one received pembrolizumab monotherapy, and one patient conceived while on combination treatment with ipilimumab plus intralesional IL-2 (aldesleukin; figure 3).[62]Four of these case reports reported intrauterine growth restriction, placental insufficiency, or both between weeks 24 and 33, for which caesarean sections were performed.[61,63-65] Two of nine neonates showed some form of congenital deficiency; one was born with congenital hypothyroidism, denoted as a possible immune-related adverse event (the normal-sized thyroid gland showed homogeneous tracer uptake), which spontaneously recovered within six months;[63] one twin was born without a left hand, most likely because of strangulation by the amniotic cord unrelated to the immunotherapy (figure 3).[65] Furthermore, one neonate suffered from typical prematurity issues, because a caesarean section had to be performed 24 weeks and 2 days due to maternal deterioration.[60] Of the five placentas that were pathologically examined,

four were negative for metastatic melanoma, [63-66] and one showed several melanoma metastases at the maternal side of the placenta[60] (histologically examine the placenta is important because placental involvement increases the fetal risk of melanoma[67]). At the most recent follow-up (between six weeks and 2.75 years), all children were healthy, had normal developmental milestones and showed no evidence of disease. [60-66]

Agents	Isotype	Target	Key preclinical findings			Key clinical findings		Use during lactation	Future pregnancy
			Physiological role in fetus	*Transplacental transmission*	*Fetotoxic studies*	*First trimester*	*Second and third timester*		
Anti-PD-1	IgG4	PD-1	PD-1 involved in establishing and maintaining feto-maternal tolerance[22]	Crosses placenta; increased transmission during second and third trimester[50,68]	No direct embryo-toxicity or teratogenicity; increased rates of growth restriction, prematurity, and embryonal, fetal and neonatal death[50]	No congenital malformations; one neonate with congenital hypothyroidism reported[63,65,66]	Intrauterine growth restriction; placental insufficiency [61,64]	No passive transmission, based on molecular size; active transmission unknown[69]	Contraception is advised for 5 months after last dose; potential endocrine adverse events for the mother
Anti-PD-L1	IgG1	PD-L1	PD-L1 involved in establishing and maintaining feto-maternal tolerance[22]	Crosses placenta; increased transmission during second and third trimester[50,68]	No direct embryo-toxicity or teratogenicity; increased rates of growth restriction, prematurity, and embryonal, fetal and neonatal death[19,49]	No data available	No data available	No passive transmission, based on molecular size; active transmission unknown[69]	Contraception is advised for 5 months after last dose; potential endocrine adverse events for the mother
Anti-CTLA-4	IgG4	PD-1	CTLA-4 is involved in feto-maternal tolerance, although less than PD-1 and PD-L1[37,39,48,50-53]	Crosses placenta, increased transmission 2nd and 3rd trimester[50,68]	No direct embryotoxicity or teratogenicity; in third trimester, increased rates of growth restriction, prematurity, and infant mortality[56-58]	No congenital malformations[62,64]	Intrauterine growth restriction, placental insufficiency[60,61]	No passive transmission, based on molecular size; one case report showed cumulative increase in breastmilk[69]	Contraception is advised for 5 months after last dose; potential endocrine adverse events for the mother
IFN-α	NA	NA	Cytokine involved in embryonic development and implantation phase[70]	Does not cross the placenta in significant amounts[71]	Increased risk of miscarriage, but only at higher doses than those used in humans; no teratogenic effects[5]	One infant born with major malformations, possibly due to concurrent imatinib exposure during first trimester[72]	No adverse events[73]	Small peak levels detects 4-5 h after intravenous administration[74]	Contraception is advised during treatment
Interleukin-2	NA	NA	Cytokine thought to be involved in maintaining fetal allograft[45]	No data available	Increased embryolethal effects at higher doses than those used in humans; [75] no evidence of teratogenicity was observed other than that attributed to maternal toxicity	No data available	No adverse events (one case report available[62])	No data available	Contraception is advised during treatment
Intravesical BCG	NA	NA	NA	No data available	No data available	No data available	No adverse events (one case report available[76])	No data available	Contraception is advised for 1 week after treatment
Intralesional talimogene laherparepvec	NA	NA	NA	Wild type HSV-1 crosses placenta[77]	No effects on embryonic or fetal development were observed at	No data available; wild-type HSV-1 infections in fetus or	No data available; wild-type HSV-1 infections in fetus or neonate can	No data available	Contraception is advised for 30 days after treatment

					doses higher than those used in humans[78]	neonate can cause multiorgan failure and death[77]	cause multiorgan failure and death[77]		
Lenalidomide, Pomalidomide	NA	CRBN	NA	Crosses placenta[79]	Extremely teratogenic[79]	Extremely teratogenic, severe birth defects in almost any organ or tissue[79]	Extremely teratogenic, severe birth defects in almost any organ or tissue[79]	No data available	Contraception is advised for 4 weeks after treatment
CAR T cell	NA	CD19, BCMA	No data available	No data available	No data available	No data available	No data available	No data available	No data available; risk on-target, off-tumour toxic effects and hypogammaglobinaemia[80-82]
Blinatumomab	NA	CD3/ CD19	NA	Crosses placenta[83]	No embryonal or fetal toxic effects or teratogenic effects observed[83]	No data available	No data available	No data available,	No data available; contraception is advised for at least 48 h after treatment

Table 1. Key preclinical and clinical findings on the use of immunotherapy during pregnancy and possible clinical implications. *CAR=chimeric antigen receptor. HSV-1=herpes simplex virus type 1. IFNα=interferon α. NA=not applicable*

Three mothers with metastatic melanoma progressed during pregnancy or shortly after delivery. [60-62] The other four patients either remained in complete remission or showed no evidence of disease after completion of their treatment (appendix 1). [63-66] Of the women who progressed, one deteriorated at 24 weeks and 2 days despite combination treatment with ipilimumab plus nivolumab, for which an emergency caesarean section was performed. The patient died the day after the caesarean section. [60] The second patient was treated with ipilimumab in combination with intralesional IL-2 and discovered she was 6 weeks pregnant after the third dose of ipilimumab, the patient received the fourth dose and an additional eight doses of low-dose intralesional aldesleukin during the first 4 months of her pregnancy. In-transit metastases progressed after discontinuation of treatment and were surgically removed during the pregnancy. The scan after delivery revealed new lymph node metastases and a recurrent in-transit metastasis, after which pembrolizumab treatment was initiated. The patient progressed further with distant metastases about 1 year later. [62] The third patient was initially treated with ipilimumab plus nivolumab, followed by one dose of nivolumab monotherapy, which was discontinued due to immune-related liver toxicity. At week 31 of pregnancy, re-evaluation with whole body MRI showed a mixed response, with improvement of liver and bone metastases, but with progression of breast and lung lesions, and two non-specific foci on the brain MRI. After delivery, she underwent surgical stabilisation of bone lesions followed by palliative radiotherapy. Three weeks later systemic treatment with the BRAF-inhibitor vemurafenib was initiated, after which notable improvement of the lesions was observed. [61]

Two patients with metastatic melanoma and the patient with a placental site trophoblastic tumour were in radiological or biochemical remission before discovery of their pregnancy and were able to discontinue their ICI treatment during the course of their pregnancy. [63,65,66] These patients remained without evidence of disease at last follow-up after delivery without resuming treatment. One patient with various sites of metastatic disease, including brain metastases, had previously received several lines of systemic treatment, stereotactic radiosurgery on two brain metastases and a resection of a brain metastasis, and was treated with ipilimumab plus nivolumab combination therapy shortly before she became pregnant. This patient received the fourth dose of combination treatment with ipilimumab plus nivolumab during her pregnancy, followed by nivolumab monotherapy. The patient experienced no immune-related adverse events, but did require intravenous iron therapy for iron-deficient anaemia. She did not show clinical signs of progression during the pregnancy, however, on the first day after delivery, she experienced a generalized tonic-clonic seizure, likely to be casued by a nodular enhancement and associated oedema in the right posterior frontal region, which was treated with intravenous dexamethasone plus levetiracetam. She underwent a craniotomy 3 weeks later, and pathological assessment revealed radiation necrosis without viable tumour cells. No other sites of active disease were observed, and the patient continued treatment with nivolumab monotherapy. [64]

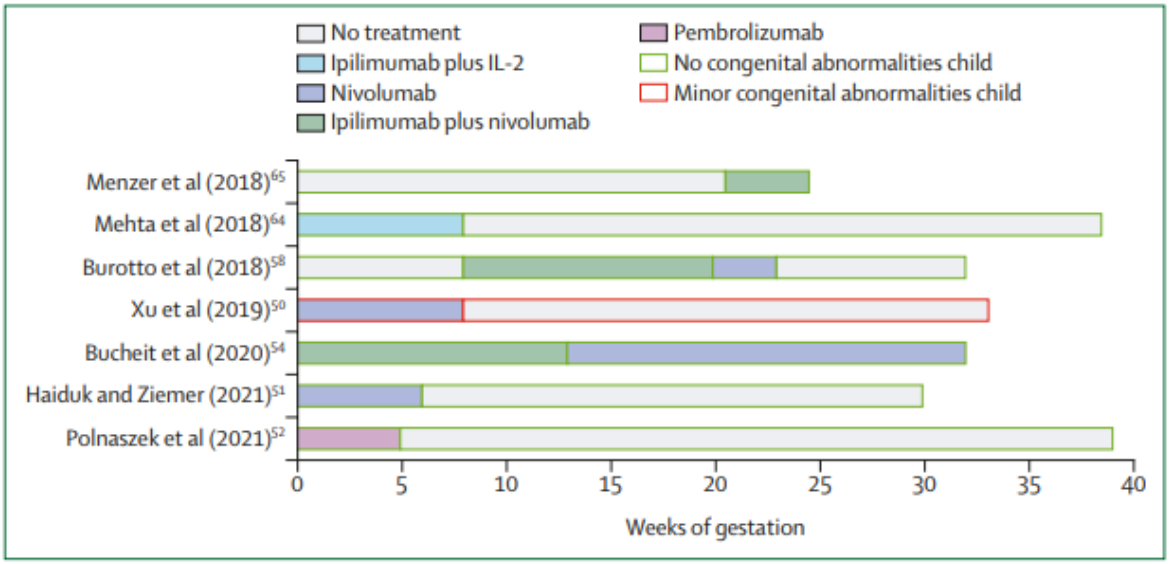


Figure 3. Overview of case reports of women treated with immune checkpoint inhibitors during pregnancy. [60-66] The *frame length indicates duration of pregnancy in each case. Bar colours indicate treatment given. Frame colours indicate pregnancy outcome (green meaning no adverse events and orange meaning minor congenital deficiencies). IL-2=interleukin 2.*

Immune-related adverse events

immune-related adverse events are common in patients treated with ICIs, especially when receiving combination therapy. [10] The toxicities can affect any organ, with varying frequencies and severities. [10] Endocrinopathies can be of particular concern when it comes to conception and future pregnancies. Immune-related adverse events are often treated with steroids. [84] Although prednisone doses up to 20mg/day are considered safe during pregnancy, most severe immune-related adverse events are treated with much higher doses (1-2mg/kg). [84,85] During pregnancy, these drugs have been associated with increased risks of gestational diabetes, fetaloral-facial clefts (first trimester exposure) and hypothalamic-pituitary-adrenal axis dysfunction. [85]

Another consideration with regard to fetal risks associated with ICI treatment during pregnancy is related to the molecular weight and IgG subtype of the monoclonal antibodies. Because their weight exceeds the limit for simple diffusion, monoclonal antibodies have to be actively transported across the placental barrier, which is most effective for IgG1, closely followed by IgG4 isotypes (table 1). [68] Because this transport mechanism is dependent on neonatal Fc receptors, which are not present during the first 14 weeks, fetuses are fairly protected during organogenesis, whereas the highest rate of transplacental transmission occurs in the late second and third trimesters. [68] Fetal exposure to ICIs might therefore induce immune-related adverse events in the neonate, as has been observed by Xu and colleagues. [63] Finally, ICI treatment often leads to increased IFNγ production, which in theory could lead to implantation failure, miscarriage, fetal stress, pre-eclampsia, and preterm labour. [29,86]

Out of the seven published case reports, two reported that patients experienced an immune-related adverse event during the course of their pregnancy (Supplementary table 1). The first patient, treated with ipilimumab plus aldesleukin, experienced grade 1 diarrhoea, for which reason the third dose of ipilimumab was

delayed. She successfully received the third and fourth doses, without recurrence or progression of immune-related symptoms. [62] The second patient developed immune-related liver toxic effects after the first dose of nivolumab monotherapy (after previous ipilimumab plus nivolumab combination therapy), requiring methylprednisolone, followed by maintenance therapy with dexamethasone and azathioprine during her pregnancy. Treatment with nivolumab was not resumed. [61] A third patient had suspected immune-related liver toxic effects before her pregnancy, which as treated with azathioprine. She was able to continue treatment with nivolumab. [65]

Future pregnancy and breastfeeding

As the indications for ICIs expand, including use in early stage of cancer as adjuvant or neoadjuvant treatment, concerns regarding their potential effect on fertility and future pregnancies are increasing. [87,88] In non-human primate models treated with pembrolizumab, nivolumab, or durvalumab, no signs of carcinogenicity or gonadotoxicity were observed. [50] Weekly administration of atezolizumab in monkeys at a dose (50 mg/kg intravenously) that was six times higher than the recommended dose in humans (800 mg intravenously once every 2 weeks) led to an irregular menstrual cycle and an absence of newly formed corpora lutea in the ovaries of monkeys. [89] This outcome was reversible upon discontinuation of treatment. Ipilimumab was shown to specifically bind to ovarian connective tissue of monkeys, but without causing histopathological changes in the ovum. [90]

Endocrinopathies are of particular concern for conception and pregnancy: therapy-induced hypophysitis occurs in less than 1–3% of patients treated with anti-PD-1 or anti-PD-L1 and in about 12% of patients treated with anti-CTLA-4. [10] Disruption of the anterior pituitary gland can lead to impaired secretion of follicle stimulating hormone and luteinizing hormone, resulting in ovulatory dysfunction or premature menopause. [10,91] In 23% of cases, this disruption lasted for 33 months or longer. [91] Hypothyroidism, commonly seen during anti-PD-1 and anti-PD-L1 treatment, can also lead to reduced fertility. During pregnancy, inadequately treated hypothyroidism has been associated with increased maternal risks including hypertension, anaemia, placental abruption, and postpartum haemorrhage and with adverse fetal outcomes such as preterm birth, low birthweight, and respiratory distress. [84,92]

So far, available information about the potential impact of ICIs on fertility shows that five patients were able to conceive while receiving treatment with ICIs (appendix 1). [62-66] One of these patients had a ten year history of infertility from unclear causes and was found to be pregnant after 14 months of nivolumab maintenance therapy. [63] Similarly, subsequent fertility after immunotherapy was unaffected in a case report by Bolze and colleagues. [93] The 27-year-old patient was succesfully treated with 11 cycles of avelumab for a chemotherapy-resistant, low-risk non-metastatic post molar gestational trophoblastic neoplasia, and became pregnant 13 months after treatment. The pregnancy was uneventful with normal fetal and placental development, and the patient did not show signs of relapse after delivery.

On the basis of the findings from both preclinical studies and clinical case reports, the risk of fetal adverse outcomes is probably dependent on the maternal immune response to the fetus rather than on direct cytotoxic effects. Therefore, the risk varies highly from patient to patient, as both the fetomaternal immune tolerance and PD-L1 expression at the utero-placental interface are correlated with the degree of fetal allogeneity. [19,27,50] However, because the clinical consequences of these findings on human reproduction are not yet fully elucidated, the National Comprehensive Cancer Network advises all patients of reproductive age to use effective contraception during and for at least five months after the last dose of immunotherapy, which corresponds to at least 5-10 half-lives depending on the drug. Of note, individual receptor occupancy might vary, depending on several factors including tumour burden and genetic polymorphisms affecting the neonatal Fc receptor. This variation means that there might be long-term ongoing functional effects of these antibodies on their targets with unknown consequences during conception or pregnancy. [94] Furthermore, the National Comprehensive Cancer Network guidelines report a contraindication for breastfeeding during and for at least five months after the final dose of ICIs. Although clear evidence of the potential harmful effects of breastfeeding during ICI treatment on infants is not available, Ross and colleagues[69] showed a cumulative increase of ICI-concentrations in the breastmilk of a patient treated with ipilimumab after giving birth. Although breastmilk concentrations were substantially lower than serum concentrations, the active drug could be detected up to three weeks after the final infusion. [69]

OTHER IMMUNOTHERAPY OPTIONS

Cytokines

The most used cytokines for cancer treatment are IFNα and IL-2. Due to the development of novel, less toxic and more targeted immunotherapies, these cytokines are rarely used nowadays.

IFNα

IFNα has been administered to pregnant patients with hematologic malignancies. Results from case reports and retrospective studies are reassuring in terms of toxic effects of the fetus (table 1). [5,73] Increased rates of spontaneous abortion were shown in animal studies with doses higher than those recommended for humans. [5] Because IFNα does not cross the placenta in substantial amounts, it is considered a safe treatment option throughout the entire pregnancy.

IL-2

Aldesleukin is a recombinant form of IL-2 that induces proliferation and maturation of T cells, and enhances tumour reactivity. [95] It increases IFNγ production, which in turn enhances antigen presentation and recognition of tumour cells. IL-2 can be administered intravenously and intralesionally. Toxic effects from systemic

high-dose IL-2 are severe and can be life-threatening, mimicking septic shock often accompanied by lymphocytopenia and eosinophilia.[95] High-dose IL-2 treatment has proven benefit in metastatic melanoma and renal cell carcinoma. Studies with recombinant IL-2 in rats showed embryolethal effects when administered at 27-36 times the clinical dose.[75] In the absence of evidence for teratogenicity, substantial maternal toxic effects were the presumed cause. Metha and colleagues[62], described the delivery of a healthy infant after eight intralesional aldesleukin injections (two per week) of 9 million international units per dose, in combination with ipilimumab. Aldesleukin should only be used during pregnancy if the potential benefits outweigh the potential fetal risks (table 1).

Vaccines

BCG-vaccination

BCG is a live, attenuated tubercle bacillus that induces local T cell-mediated immunity responses. It is approved as the primary treatment for intermediate and high-risk non-muscle invasive bladder cancer. Animal reproduction studies involving BCG treatment have not been done. Systemic absorption after intravesical administration is low, but can increase with bladder damage. One case of BCG therapy in a pregnant woman was reported by Wax and colleagues.[76] Starting at 13 weeks of gestation, six weekly intravesical BCG vaccinations were administered without complications. After a spontaneous vaginal delivery at 39 weeks, normal neonatal outcomes were observed until the last follow-up at three months of age.[76] On the basis of the scarcity of experience with live attenuated vaccines during pregnancy, these are contraindicated. However, intravesical BCG therapy can be considered because the risks seem to be low (table 1).

Tamoligene laherparepvec

Intralesional talimogeen laherparepvec was the first oncolytic immunotherapy approved for local treatment of unresectable melanoma. It is a genetically engineered herpes simplex virus type 1 (HSV-1) that selectively replicates in tumour tissue, lyses tumour cells and promotes antitumour immunity. When administered to immunocompetent pregnant mice during organogenesis at 60 times (400 million plaque-forming units per kg) the maximum clinical dose, minimal transmission of talimogeen laherparepvec into fetal blood and no embryonic or fetal developmental toxic effects were observed.[78] Wild type HSV-1 infections have been observed in patients receiving talimogeen laherparepvec.[78] During pregnancy, HSV-1 has the potential to cross the placental barrier and there is a risk of vaginal transmission during birth, which can cause serious adverse effects in the fetus, including multiorgan failure and death.[77] Although the herpetic infections caused by talimogeen laherparepvec are unlikely as severe as wild type HSV-1 infections, due to unknown fetal risks, talimogeen laherparepvec should be avoided during pregnancy when possible(table 1).

Immunomodulatory drugs

Lenalidomide and pomalidomide are immunomodulatory drugs approved for the treatment of several haematological malignancies. They are derivatives of thalidomide, a drug that is denoted as extremely teratogenic after reports showed severe birth defects in more than 10 000 children born after in utero thalidomide exposure between 1957 and 1962. [79] Because of these reports, these drugs are strictly contraindicated during pregnancy, and effective contraception should be used for four weeks after completion of treatment should be used (table 1).

Adoptive cell therapies

At present, chimeric antigen receptor (CAR) modified T cell therapies that target CD19 and B-cell maturation antigen are the only approved adoptive cell therapies and are used to treat certain haematological malignancies. Currently, no data regarding their use during pregnancy are available, nor is any information available from reproductive developmental toxicity studies in animal models(table 1). Because of the absence of data and the complexity of this treatment which often requires non-myeloablative but lymphodepleting chemotherapy preconditioning, simultaneous pregnancy should be avoided.

Bispecific T-cell engagers

Blinatumomab is a CD19 and CD3 bispecific T-cell engager used for the treatment of adults and children with relapsed or refractory B-cell precursor acute lymphoblastic leukaemia. So far, no animal reproduction studies have been done and no case reports about its use during pregnancy have been published. Treatment of mice with a murine surrogate molecule during organogenesis showed that it can cross the placental barrier, but did not cause any embryonic or fetal toxic effects or teratogenity. [83] The pregnant mice showed depletion of B-cells; although no haematological assessments were done on the fetuses, B-cell lymphocytopenia can be expected following exposure in utero. [83] Because of the unknown risk of (major) birth defects and miscarriages, use during pregnancy is contraindicated. Effective contraception should be used during treatment and for at least 48h after treatment with blinatumomab. [83]

Future pregnancy and breastfeeding

No information is available about fertility after treatment with cytokines, vaccines, immunomodulatory drugs and bispecific T-cell engagers. Because long term adverse events are unknown, recommendations regarding timing of pregnancy are based on the half-lives of these agents (table 1).

CAR T-cell treatments are not considered first-line treatments. As such, we expect that cases of CAR T-cell therapy during pregnancy will be extremely rare. Pregnancy following CAR T-cell therapy is a more probable scenario because young female patients that might have been cured of acute lymphoblastic leukaemia after CD19- targeting CAR T-cell therapy might have a current or future desire to get pregnant. In this scenario, considering that genetically modified cells can have a very long in-vivo lifespan is important: persistence up to

several years has been described.[96] Therefore, even patients treated at a young age might still have the adoptive therapy cells in their body at the time of conception and pregnancy. Some targets might not be expressed on healthy cells in the non- pregnant state, whereas they might become expressed on the placenta, umbilical cord, or in the developing fetus (ie, cancer testis antigens) with unknown consequences and potential on-target, off-tumour toxic effects for both mother and child.[80,81] Furthermore, a specific consequence of treatment with CD19-targeting CAR T cells is prolonged B-cell aplasia with hypogammaglobinaemia,[82] which can result in an increased risk of both maternal and neonatal infections.

Low concentrations of IFNα are transferred into breastmilk, with small peak concentrations detectable 4–5 h after intravenous administration.[74] No information is available on the concentrations of aldesleukin, BCG, talimogene laherparepvec, thalidomide or its derivatives, CAR T cells, and bispecific T-cell engagers excreted in breastmilk; therefore, breastfeeding during these therapies should be discouraged.

CONCLUDING REMARKS AND RECOMMENDATIONS FOR FUTURE CLINICAL TRIALS

Because immunotherapies are fairly new treatment options in oncology, information on their use during pregnancy is scarce. In this Review, we summarised the potential risks and possibilities per subgroup of immuno- therapies. Until comprehensive studies are done, the evidence is based only on theoretical assumptions, preclinical studies, and case reports.

In view of the largely unknown risks, treatment with immunotherapy during pregnancy should be carefully considered in light of the risk–benefit ratio per individual patient. The risk is likely to vary per patient, in particular with regards to ICIs because this risk is correlated with the degree of fetal allogeneity.

Where possible, delivery at term (from 37 weeks) in pregnant patients with cancer should be pursued. However, closely monitoring both maternal treatment response and prognosis and fetal development during the course of the pregnancy is of vital importance. Optimal timing of delivery should be decided on a case- by-case basis. For certain drugs, increased transplacental transmission rates might occur from the late second trimester onwards. Depending on the half-lives of the used compounds, temporary discontinuation before delivery (if allowed by the maternal clinical condition) could be considered. Furthermore, special attention should be paid to patients with metastatic melanomas because of the risks of placental or fetal metastases with non-response and disease progression, which might increase with gestational age.

This Review helps clinicians to discuss the associated risks and considerations with the patient and her family. Due to the rarity of cancer during pregnancy and the very limited experience with immunotherapy treatment during pregnancy, treatment in a multidisciplinary setting and close monitoring of both mother and fetus throughout the course of the pregnancy and after delivery should be encouraged, preferably in a specialised medical centre. Furthermore, such cases should be discussed in specialised multidisciplinary tumour boards, including not only oncological disciplines but also perinatal and paediatric specialists. To expand the

knowledge about the treatment of pregnant women, clinicians should be encouraged to report known cases and to register their patients in national and international registries.

REFERENCES

1 Lee, Y. Y. *et al.* Incidence and outcomes of pregnancy-associated cancer in Australia, 1994-2008: a population-based linkage study. *Bjog* **119**, 1572-1582 (2012).
2 Stensheim, H., Moller, B., van Dijk, T. & Fossa, S. D. Cause-specific survival for women diagnosed with cancer during pregnancy or lactation: a registry-based cohort study. *Journal of Clinical Oncology* **27**, 45-51 (2009).
3 Lenaerts, L., Jatsenko, T., Amant, F. & Robert Vermeesch, J. Noninvasive Prenatal Testing and Detection of Occult Maternal Malignancies. *Clinical chemistry* **65**, 1484-1486 (2019).
4 Kal, H. B. & Struikmans, H. Radiotherapy during pregnancy: fact and fiction. *The Lancet. Oncology* **6**, 328-333 (2005).
5 NTP Monograph: Developmental Effects and Pregnancy Outcomes Associated With Cancer Chemotherapy Use During Pregnancy. *NTP Monogr*, i-214 (2013).
6 van Gerwen, M. *et al.* Association of Chemotherapy Timing in Pregnancy With Congenital Malformation. *JAMA Netw Open* **4**, e2113180 (2021).
7 Lambertini, M., Peccatori, F. A. & Azim, H. A., Jr. Targeted agents for cancer treatment during pregnancy. *Cancer treatment reviews* **41**, 301-309 (2015).
8 Chaplin, D. D. Overview of the immune response. *J Allergy Clin Immunol* **125**, S3-23 (2010).
9 Lu, B. & Finn, O. J. T-cell death and cancer immune tolerance. *Cell Death & Differentiation* **15**, 70-79 (2008).
10 Martins, F. *et al.* Adverse effects of immune-checkpoint inhibitors: epidemiology, management and surveillance. *Nature reviews. Clinical oncology* **16**, 563-580 (2019).
11 Ozen, M., Novak, C. & Burd, I. Placenta immune infiltrates and perinatal outcomes. *Am J Reprod Immunol* **79**, e12850 (2018).
12 Fuhler, G. M. The immune system and microbiome in pregnancy. *Best Pract Res Clin Gastroenterol* **44-45**, 101671 (2020).
13 Mor, G., Cardenas, I., Abrahams, V. & Guller, S. Inflammation and pregnancy: the role of the immune system at the implantation site. *Ann N Y Acad Sci* **1221**, 80-87 (2011).
14 Dutta, S. & Sengupta, P. Defining pregnancy phases with cytokine shift. *Journal of Pregnancy and Reproduction* **1** (2017).
15 Hsu, P. & Nanan, R. K. Innate and adaptive immune interactions at the fetal-maternal interface in healthy human pregnancy and pre-eclampsia. *Front Immunol* **5**, 125 (2014).
16 Yang, F., Zheng, Q. & Jin, L. Dynamic Function and Composition Changes of Immune Cells During Normal and Pathological Pregnancy at the Maternal-Fetal Interface. *Frontiers in Immunology* **10** (2019).
17 Erlebacher, A. Immunology of the maternal-fetal interface. *Annu Rev Immunol* **31**, 387-411 (2013).
18 Trundley, A. & Moffett, A. Human uterine leukocytes and pregnancy. *Tissue Antigens* **63**, 1-12 (2004).
19 Guleria, I. *et al.* A critical role for the programmed death ligand 1 in fetomaternal tolerance. *J Exp Med* **202**, 231-237 (2005).
20 Hackmon, R. *et al.* Definitive class I human leukocyte antigen expression in gestational placentation: HLA-F, HLA-E, HLA-C, and HLA-G in extravillous trophoblast invasion on placentation, pregnancy, and parturition. *Am J Reprod Immunol* **77** (2017).
21 Blaschitz, A., Hutter, H. & Dohr, G. HLA Class I protein expression in the human placenta. *Early Pregnancy* **5**, 67-69 (2001).
22 Sharpe, A. H., Wherry, E. J., Ahmed, R. & Freeman, G. J. The function of programmed cell death 1 and its ligands in regulating autoimmunity and infection. *Nat Immunol* **8**, 239-245 (2007).
23 Nagamatsu, T., Schust, D. J., Sugimoto, J. & Barrier, B. F. Human decidual stromal cells suppress cytokine secretion by allogenic CD4+ T cells via PD-1 ligand interactions. *Hum Reprod* **24**, 3160-3171 (2009).
24 Meggyes, M., Miko, E., Szigeti, B., Farkas, N. & Szereday, L. The importance of the PD-1/PD-L1 pathway at the maternal-fetal interface. *BMC pregnancy and childbirth* **19**, 74 (2019).
25 Fife, B. T. & Pauken, K. E. The role of the PD-1 pathway in autoimmunity and peripheral tolerance. *Ann N Y Acad Sci* **1217**, 45-59 (2011).
26 Holets, L. M., Hunt, J. S. & Petroff, M. G. Trophoblast CD274 (B7-H1) is differentially expressed across gestation: influence of oxygen concentration. *Biol Reprod* **74**, 352-358 (2006).
27 Zhang, Y. H., Tian, M., Tang, M. X., Liu, Z. Z. & Liao, A. H. Recent Insight into the Role of the PD-1/PD-L1 Pathway in Feto-Maternal Tolerance and Pregnancy. *Am J Reprod Immunol* **74**, 201-208 (2015).
28 Sayama, S. *et al.* Human decidual macrophages suppress IFN-γ production by T cells through costimulatory B7-H1:PD-1 signaling in early pregnancy. *J Reprod Immunol* **100**, 109-117 (2013).

29 Murphy, S. P. *et al.* Interferon gamma in successful pregnancies. *Biol Reprod* **80**, 848-859 (2009).
30 Banerjee, S. *et al.* Placental Expression of Interferon-γ (IFN-γ) and Its Receptor IFN-γR2 Fail to Switch from Early Hypoxic to Late Normotensive Development in Preeclampsia. *The Journal of Clinical Endocrinology & Metabolism* **90**, 944-952 (2005).
31 Clark, D. A., Chaouat, G., Arck, P. C., Mittruecker, H. W. & Levy, G. A. Cytokine-dependent abortion in CBA x DBA/2 mice is mediated by the procoagulant fgl2 prothrombinase [correction of prothombinase]. *J Immunol* **160**, 545-549 (1998).
32 Wing, K. *et al.* CTLA-4 control over Foxp3+ regulatory T cell function. *Science* **322**, 271-275 (2008).
33 Zhang, Y. H. & Sun, H. X. Immune checkpoint molecules in pregnancy: Focus on regulatory T cells. *Eur J Immunol* **50**, 160-169 (2020).
34 Somerset, D. A., Zheng, Y., Kilby, M. D., Sansom, D. M. & Drayson, M. T. Normal human pregnancy is associated with an elevation in the immune suppressive CD25+ CD4+ regulatory T-cell subset. *Immunology* **112**, 38-43 (2004).
35 Nancy, P. *et al.* Chemokine Gene Silencing in Decidual Stromal Cells Limits T Cell Access to the Maternal-Fetal Interface. *Science* **336**, 1317-1321 (2012).
36 Jin, L. P., Fan, D. X., Zhang, T., Guo, P. F. & Li, D. J. The costimulatory signal upregulation is associated with Th1 bias at the maternal-fetal interface in human miscarriage. *Am J Reprod Immunol* **66**, 270-278 (2011).
37 Sasaki, Y. *et al.* Decidual and peripheral blood CD4+CD25+ regulatory T cells in early pregnancy subjects and spontaneous abortion cases. *Mol Hum Reprod* **10**, 347-353 (2004).
38 Zhao, Y., Zheng, Q. & Jin, L. The Role of B7 Family Molecules in Maternal-Fetal Immunity. *Front Immunol* **11**, 458 (2020).
39 Aluvihare, V. R., Kallikourdis, M. & Betz, A. G. Regulatory T cells mediate maternal tolerance to the fetus. *Nat Immunol* **5**, 266-271 (2004).
40 Saito, S., Nakashima, A., Shima, T. & Ito, M. Th1/Th2/Th17 and regulatory T-cell paradigm in pregnancy. *Am J Reprod Immunol* **63**, 601-610 (2010).
41 Mosmann, T. R., Cherwinski, H., Bond, M. W., Giedlin, M. A. & Coffman, R. L. Two types of murine helper T cell clone. I. Definition according to profiles of lymphokine activities and secreted proteins. 1986. *J Immunol* **175**, 5-14 (2005).
42 Wegmann, T. G., Lin, H., Guilbert, L. & Mosmann, T. R. Bidirectional cytokine interactions in the maternal-fetal relationship: is successful pregnancy a TH2 phenomenon? *Immunol Today* **14**, 353-356 (1993).
43 Piccinni, M. P. *et al.* How pregnancy can affect autoimmune diseases progression? *Clin Mol Allergy* **14**, 11 (2016).
44 Chaouat, G. *et al.* Cytokines, implantation and early abortion: re-examining the Th1/Th2 paradigm leads to question the single pathway, single therapy concept. *Am J Reprod Immunol* **50**, 177-186 (2003).
45 Burns, D. N. *et al.* Changes in immune activation markers during pregnancy and postpartum. *J Reprod Immunol* **42**, 147-165 (1999).
46 Sutton, M. Y. *et al.* Effect of pregnancy and human immunodeficiency virus infection on intracellular interleukin-2 production patterns. *Clin Diagn Lab Immunol* **11**, 780-785 (2004).
47 Zeng, W. *et al.* PDL1 blockage increases fetal resorption and Tfr cells but does not affect Tfh/Tfr ratio and B-cell maturation during allogeneic pregnancy. *Cell death & disease* **11**, 119 (2020).
48 Zenclussen, A. C. *et al.* Abnormal T-cell reactivity against paternal antigens in spontaneous abortion: adoptive transfer of pregnancy-induced CD4+CD25+ T regulatory cells prevents fetal rejection in a murine abortion model. *Am J Pathol* **166**, 811-822 (2005).
49 Habicht, A. *et al.* A link between PDL1 and T regulatory cells in fetomaternal tolerance. *J Immunol* **179**, 5211-5219 (2007).
50 Poulet, F. M., Wolf, J. J., Herzyk, D. J. & DeGeorge, J. J. An Evaluation of the Impact of PD-1 Pathway Blockade on Reproductive Safety of Therapeutic PD-1 Inhibitors. *Birth defects research. Part B, Developmental and reproductive toxicology* **107**, 108-119 (2016).
51 Simpson, T. R. *et al.* Fc-dependent depletion of tumor-infiltrating regulatory T cells co-defines the efficacy of anti-CTLA-4 therapy against melanoma. *J Exp Med* **210**, 1695-1710 (2013).
52 Quezada, S. A. & Peggs, K. S. Lost in Translation: Deciphering the Mechanism of Action of Anti-human CTLA-4. *Clinical Cancer Research* **25**, 1130-1132 (2019).
53 Buchbinder, E. I. & Desai, A. CTLA-4 and PD-1 Pathways: Similarities, Differences, and Implications of Their Inhibition. *Am J Clin Oncol* **39**, 98-106 (2016).
54 Miwa, N. *et al.* IDO expression on decidual and peripheral blood dendritic cells and monocytes/macrophages after treatment with CTLA-4 or interferon-gamma increase in normal pregnancy but decrease in spontaneous abortion. *Mol Hum Reprod* **11**, 865-870 (2005).
55 Li, W. *et al.* CTLA4Ig gene transfer alleviates abortion in mice by expanding CD4+CD25+ regulatory T cells and inducing indoleamine 2,3-dioxygenase. *J Reprod Immunol* **80**, 1-11 (2009).

56 Bugelski, P. J. & Martin, P. L. Concordance of preclinical and clinical pharmacology and toxicology of therapeutic monoclonal antibodies and fusion proteins: cell surface targets. *Br J Pharmacol* **166**, 823-846 (2012).
57 Kristinsson, S. Y., Gridley, G., Hoover, R. N., Check, D. & Landgren, O. Long-term risks after splenectomy among 8,149 cancer-free American veterans: a cohort study with up to 27 years follow-up. *Haematologica* **99**, 392-398 (2014).
58 Wang, S. *et al.* Blockade of CTLA-4 and Tim-3 pathways induces fetal loss with altered cytokine profiles by decidual CD4(+)T cells. *Cell death & disease* **10**, 15 (2019).
59 Marin-Acevedo, J. A., Kimbrough, E. O. & Lou, Y. Next generation of immune checkpoint inhibitors and beyond. *J Hematol Oncol* **14**, 45 (2021).
60 Menzer, C. *et al.* Immunotherapy with ipilimumab plus nivolumab in a stage IV melanoma patient during pregnancy. *Eur J Cancer* **104**, 239-242 (2018).
61 Burotto, M. *et al.* Viable Pregnancy in a patient with metastatic melanoma treated with double checkpoint immunotherapy. *Seminars in oncology* **45**, 164-169 (2018).
62 Mehta, A., Kim, K. B. & Minor, D. R. Case Report of a Pregnancy During Ipilimumab Therapy. *Journal of global oncology* **4**, 1-3 (2018).
63 Xu, W., Moor, R. J., Walpole, E. T. & Atkinson, V. G. Pregnancy with successful foetal and maternal outcome in a melanoma patient treated with nivolumab in the first trimester: case report and review of the literature. *Melanoma Res* **29**, 333-337 (2019).
64 Bucheit, A. D., Hardy, J. T., Szender, J. B. & Glitza Oliva, I. C. Conception and viable twin pregnancy in a patient with metastatic melanoma while treated with CTLA-4 and PD-1 checkpoint inhibition. *Melanoma Res* **30**, 423-425 (2020).
65 Haiduk, J. & Ziemer, M. Pregnancy in a patient with metastatic uveal melanoma treated with nivolumab. *J Dtsch Dermatol Ges* (2021).
66 Polnaszek, B., Mullen, M., Bligard, K., Raghuraman, N. & Massad, L. S. Term Pregnancy After Complete Response of Placental Site Trophoblastic Tumor to Immunotherapy. *Obstetrics & Gynecology* **138**, 115-118 (2021).
67 Alexander, A. *et al.* Metastatic melanoma in pregnancy: risk of transplacental metastases in the infant. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology* **21**, 2179-2186 (2003).
68 Pentsuk, N. & van der Laan, J. W. An interspecies comparison of placental antibody transfer: new insights into developmental toxicity testing of monoclonal antibodies. *Birth defects research. Part B, Developmental and reproductive toxicology* **86**, 328-344 (2009).
69 Ross, E. *et al.* Therapeutic monoclonal antibodies in human breast milk: a case study. *Melanoma Res* **24**, 177-180 (2014).
70 Yockey, L. J. & Iwasaki, A. Interferons and Proinflammatory Cytokines in Pregnancy and Fetal Development. *Immunity* **49**, 397-412 (2018).
71 Pons, J. C., Lebon, P., Frydman, R. & Delfraissy, J. F. Pharmacokinetics of interferon-alpha in pregnant women and fetoplacental passage. *Fetal Diagn Ther* **10**, 7-10 (1995).
72 Pye, S. M. *et al.* The effects of imatinib on pregnancy outcome. *Blood* **111**, 5505-5508 (2008).
73 Mubarak, A. A. *et al.* Normal outcome of pregnancy in chronic myeloid leukemia treated with interferon-alpha in 1st trimester: report of 3 cases and review of the literature. *Am J Hematol* **69**, 115-118 (2002).
74 Kumar, A. R., Hale, T. W. & Mock, R. E. Transfer of interferon alfa into human breast milk. *J Hum Lact* **16**, 226-228 (2000).
75 Prometheus Laboratories. PROLEUKIN (aldesleukin). July, 2012. https://www.accessdata.fda.gov/drugsatfda_docs/label/2012/103293s5130lbl.pdf (accessed April 21, 2021).
76 Wax, J. R., Ross, J., Marotto, L., Pinette, M. G. & Blackstone, J. Nonbilharzial bladder carcinoma complicating pregnancy--treatment with bacille Calmette-Guérin. *Am J Obstet Gynecol* **187**, 239-240 (2002).
77 James, S. H. & Kimberlin, D. W. Neonatal Herpes Simplex Virus Infection. *Infect Dis Clin North Am* **29**, 391-400 (2015).
78 Amgen. IMLYGIC (talimogene laherparepvec). October, 2015. https://www.fda.gov/media/94129/download (accessed April 21, 2021).
79 Ward, S. P. Thalidomide and congenital abnormalities. *Br Med J* **2**, 646-647 (1962).
80 Jungbluth, A. A. *et al.* Expression of cancer-testis (CT) antigens in placenta. *Cancer Immun* **7**, 15 (2007).
81 Gjerstorff, M. F., Kock, K., Nielsen, O. & Ditzel, H. J. MAGE-A1, GAGE and NY-ESO-1 cancer/testis antigen expression during human gonadal development. *Hum Reprod* **22**, 953-960 (2007).
82 Doan, A. & Pulsipher, M. A. Hypogammaglobulinemia due to CAR T-cell therapy. *Pediatr Blood Cancer* **65** (2018).

83 Legut, M., Dolton, G., Mian, A. A., Ottmann, O. G. & Sewell, A. K. CRISPR-mediated TCR replacement generates superior anticancer transgenic T cells. *Blood* **131**, 311-322 (2018).
84 Haanen, J. *et al.* Management of toxicities from immunotherapy: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* **28**, iv119-iv142 (2017).
85 Ponticelli, C. & Moroni, G. Fetal Toxicity of Immunosuppressive Drugs in Pregnancy. *J Clin Med* **7** (2018).
86 Ni, L. & Lu, J. Interferon gamma in cancer immunotherapy. *Cancer Med* **7**, 4509-4516 (2018).
87 Anderson, R. A. *et al.* ESHRE guideline: female fertility preservation. *Hum Reprod Open* **2020**, hoaa052 (2020).
88 Lambertini, M. *et al.* Fertility preservation and post-treatment pregnancies in post-pubertal cancer patients: ESMO Clinical Practice Guidelines(†). *Ann Oncol* **31**, 1664-1678 (2020).
89 Genentech. TECENTRIQ (atezolizumab). August, 2018. https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/761034s010lbl.pdf (accessed Aug 11, 2021).
90 Walter, J. R., Xu, S., Paller, A. S., Choi, J. N. & Woodruff, T. K. Oncofertility considerations in adolescents and young adults given a diagnosis of melanoma: Fertility risk of Food and Drug Administration-approved systemic therapies. *J Am Acad Dermatol* **75**, 528-534 (2016).
91 Albarel, F. *et al.* Long-term follow-up of ipilimumab-induced hypophysitis, a common adverse event of the anti-CTLA-4 antibody in melanoma. *Eur J Endocrinol* **172**, 195-204 (2015).
92 Abalovich, M. *et al.* Overt and subclinical hypothyroidism complicating pregnancy. *Thyroid* **12**, 63-68 (2002).
93 Bolze, P. A. *et al.* Successful pregnancy in a cancer patient previously cured of a gestational trophoblastic tumor by immunotherapy. *Ann Oncol* **31**, 823-825 (2020).
94 Centanni, M., Moes, D. J. A. R., Trocóniz, I. F., Ciccolini, J. & van Hasselt, J. G. C. Clinical Pharmacokinetics and Pharmacodynamics of Immune Checkpoint Inhibitors. *Clinical Pharmacokinetics* **58**, 835-857 (2019).
95 Amaria, R. N., Reuben, A., Cooper, Z. A. & Wargo, J. A. Update on use of aldesleukin for treatment of high-risk metastatic melanoma. *Immunotargets Ther* **4**, 79-89 (2015).
96 Porter, D. L. *et al.* Chimeric antigen receptor T cells persist and induce sustained remissions in relapsed refractory chronic lymphocytic leukemia. *Sci Transl Med* **7**, 303ra139 (2015).

Chapter 11 Severe immune-related enteritis after in utero exposure to pembrolizumab

Manuel Baarslag[*], **Joosje Heimovaara**[*], Jessica Borgers[*], Koen van Aerde, Hans Koenen, Ruben Smeets, Pauline Buitelaar, Dick Pluim, Shoko Vos, Stefanie henriet, Jan Willem de Groot, Martine van Grotel, Hilde Rosing, Jos Beijnen, Alwin Huitema, John Haanen, Frédéric Amant[#], Nicole Gierenz[#]

New England Journal of Medicine, December 2023
[*] Contributed equally to the manuscript
[#] Contributed equally to the manuscript

ABSTRACT

Immune checkpoint blockade has become standard treatment for many types of cancer. Such therapy is indicated most often in patients with advanced or metastatic disease but has been increasingly used as adjuvant therapy in those with early-stage disease. Adverse events include immune-related organ inflammation resembling autoimmune diseases. We describe a case of severe immune-related gastro-enterocolitis in a 4-month-old infant who presented with intractable diarrhea and failure to thrive after in utero exposure to pembrolizumab. Known causes of the symptoms were ruled out, and the diagnosis of pembrolizumab-induced immune-related gastro-enterocolitis was supported by the results of histopathological assays, immunophenotyping, and analysis of the level of antibodies against programmed cell death protein 1 (PD-1). The infant's condition was successfully treated with prednisolone and infliximab.

INTRODUCTION

The introduction of immune checkpoint inhibitors has improved the outcomes of patients with advanced-stage cancers, including melanoma. By targeting the pathway consisting of programmed cell death protein 1 (PD-1) and its ligand (PD-L1), anti–PD-1 monoclonal antibodies can enhance T-cell–mediated antitumor responses. However, during the targeting of this pathway, subsequent immune activation can lead to immune-related adverse events as a result of the loss of peripheral tolerance. [1]

During pregnancy, the administration of immune checkpoint inhibitors may lead to problems in the establishment and maintenance of fetal–maternal immune tolerance. [2] Concern is based on preclinical data showing transplacental transfer of these monoclonal antibodies, resulting in increased risks of spontaneous resorption, fetal growth restriction, and neonatal death. [3,4] To date, the 14 reported cases of exposure to immune checkpoint inhibitors during pregnancy have had reassuring outcomes, but in most of these cases, fetal exposure occurred in the first or second trimester, often with termination of pregnancy or preterm delivery. [5-8] During the earlier prenatal period, the fetal effect would be minimal because of the absence of IgG-transporting neonatal Fc receptors on the placenta during the first 14 weeks of pregnancy. [4] As a result of this receptor dependency, the highest transplacental transfer of antibodies against PD-1 occurs during the third trimester, with fetal IgG levels that typically exceed maternal levels at term. [4,9] Therefore, it is hypothesized that fetal or infantile immune-related adverse events are more likely to occur when maternal treatment takes place during the latter portion of the second trimester or later, with risks increasing with gestational age. [4,9] Here, we report a case of severe immune-related gastro-enterocolitis in an infant after in utero exposure to the anti–PD-1 agent pembrolizumab from the second trimester until the late third trimester for the maternal treatment of advanced-stage melanoma.

CASE DESCRIPTION

A 26-year-old woman received a diagnosis of superficial spreading melanoma on her right thigh, a lesion that was classified as stage IIIB according to the criteria of the American Joint Committee on Cancer protocol, version 8. After excision and sentinel-node removal (which revealed two positive lymph nodes), adjuvant treatment was discussed. However, at that time, ultrasonography showed a viable, intrauterine pregnancy at 9 weeks' gestation. After extensive, multidisciplinary discussion about the risks and benefits of adjuvant treatment with immune checkpoint inhibitors during pregnancy and taking into account the patient's strong desire to receive the treatment, we decided to start immunotherapy while maintaining the pregnancy. The first pembrolizumab dose (400 mg every 6 weeks) was administered at 16 weeks' gestation. After 4 months of treatment, laboratory results showed a normal level of thyroid-stimu- lating hormone (2 mU per liter [reference range, 0.40 to 4.00]), a decreased level of free thyroxine (8.3 pmol per liter [reference range, 10 to 24]), and a decreased level of cortisol (67 nmol per liter [reference range, 70 to 500]). The decreased levels of free thyroxine and cortisol could not be fully explained by gestational changes alone. An immune-mediated

hypophysitis or adrenalitis was suspected, and hydrocortisone was started pragmatically at 35 weeks' gestation.

At 37 weeks' gestation, which was 3 weeks after the last pembrolizumab administration, labor was induced because of maternal cholestasis. A healthy boy was born by uncomplicated vaginal birth, with a weight of 3300 g (z score, −0.7) and Apgar scores of 10 and 10 at 1 and 5 minutes, respectively. Macroscopic and microscopic examination of the placenta showed no abnormalities. Follow-up of the formula-fed child at 8 weeks of age showed normal weight gain, absence of congenital malformations, unremarkable physical and neurologic examinations, and normal abdominal ultrasound findings, blood counts, and thyroid and liver function.

At the age of 4 months, the child was referred to a local hospital with a history of watery diarrhea for 3 weeks, weight loss of 6%, decreased oral intake, and vomiting (Fig. 1). At presentation, besides dehydration and a distended abdomen, no significant abnormalities were found, except for a positive test for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (Table 1 and Table S1 in the Supplementary Appendix). After rehydration with oral solution and withholding of feeding, the diarrhea decreased. However, upon reintroduction of normal formula milk, the infant's symptoms recurred. To exclude a cow's milk allergy, clinicians unsuccessfully switched his feeding to an amino acid–based formula. As his weight decreased further, the patient was transferred to a tertiary medical center for further evaluation.

Total parenteral nutrition was started when the infant was 4.5 months of age, which led to reduced diarrhea, indicating that the diarrhea had both osmotic and secretory components. A broad differential diagnosis of intractable diarrhea of infancy was investigated. Two weeks later, severe hypoalbuminemia (11 g per liter [reference range, 25 to 50]) was detected, with concomitant hypogammaglobulinemia (IgG not detect- able), which suggested protein-losing enteropathy that was possibly caused by inflammation.

This hypothesis was supported by the results of gastroduodenal and subtotal colonoscopy, which showed hyperemic mucosa in the stomach, duodenum, and colon. Histologic analysis revealed total villous atrophy, chronic inflammation, and increased apoptosis in duodenal crypts as well as reactive changes in the stomach, sigmoid, and rectum (Fig. 1 and Fig. S1). These histologic changes in the duodenum were not entirely specific but strongly resembled anti– PD-1–associated immune-related gastrointestinal toxicity and colitis in adult patients.[10,11] In the literature, a similar inflammatory pattern consisting of increased lymphoplasmacytic infiltrate in the lamina propria, neutrophilic activity, and villous atrophy in the duodenum has been associated with the receipt of immune check- point inhibitors.[12-14] Autoimmune enteropathy could not be ruled out, but the characteristic finding of loss of both goblet and Paneth cells was not seen.

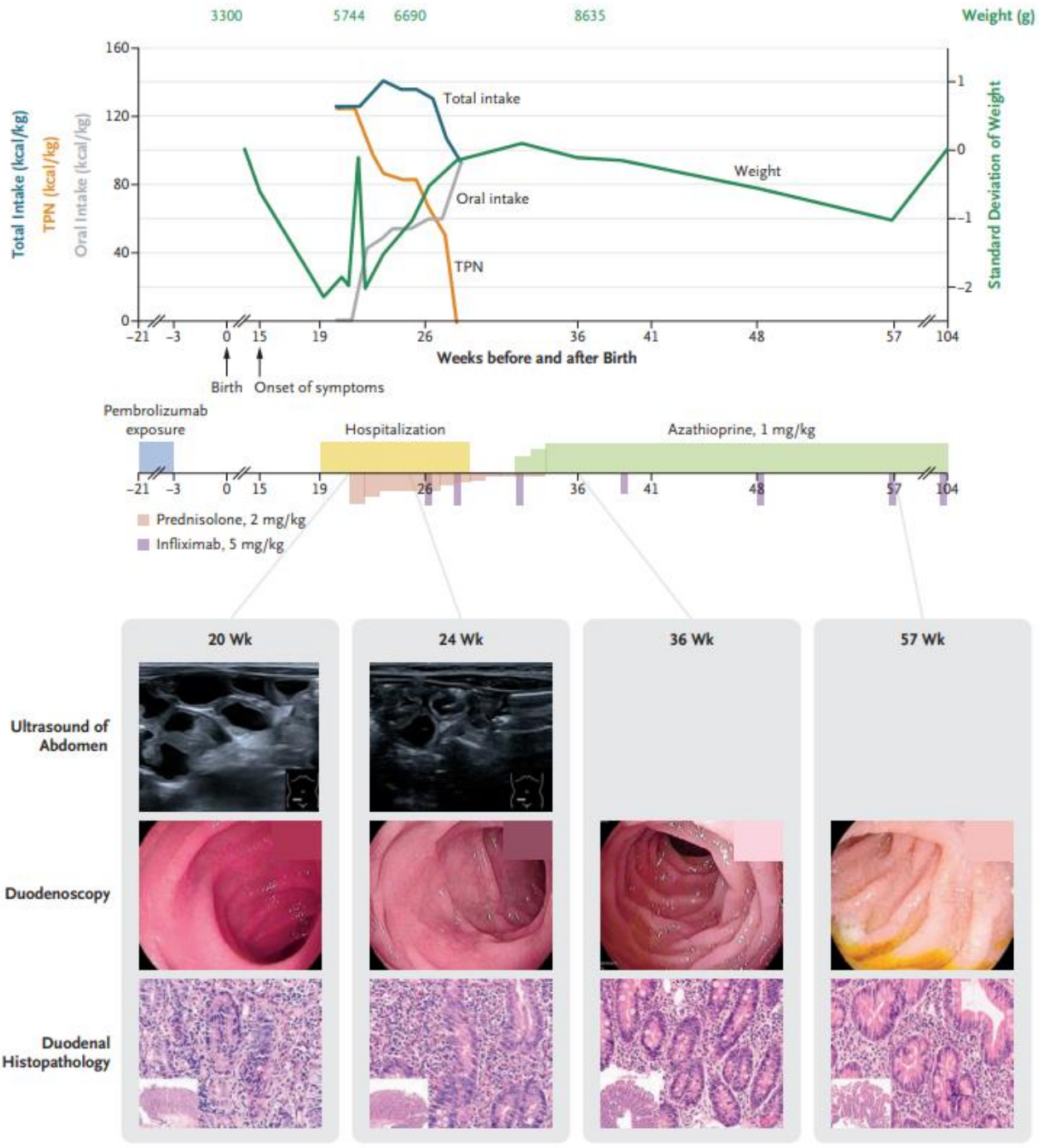


Figure 1. Overview of the Infant's Clinical Course. Shown is the clinical course of the diagnosis and treatment of severe immune-related gastroenterocolitis in a 4-month-old infant who presented with intractable diarrhea and failure to thrive after in utero exposure to pembrolizumab. Abdominal ultrasonography at 20 weeks' gestation showed a dilated small intestine with thickening of the small-bowel wall without signs of intestinal obstruction. Duodenoscopy showed hyperemia of flattened duodenal mucosa. The first histopathological biopsy of the duodenum showed complete villous atrophy, chronic active inflammation, and increased apoptosis in crypts. Prednisolone was started at 2 mg per kilogram of body weight and was tapered until 34 weeks of age. After the start of prednisolone, a single dose of furosemide was given at 22 weeks of age to treat fluid retention. Abdominal ultrasonography at 24 weeks showed the absence of dilatation or thickening of the small-bowel wall. Duodenoscopy showed less hyperemic mucosa than before. The second histopathological evaluation showed complete villous atrophy and a slight decrease in chronic active inflammation and apoptotic cells. Because of the ongoing inflammation, infliximab (at a dose of 5 mg per kilogram) was added at 26 weeks of age. At 36 weeks of age, duodenoscopy was normal and the histopathological evaluation showed partial villous atrophy and mild, chronic, focally active inflammation. Duodenoscopy at 57 weeks of age showed normal mucosa with visible villous pattern. The histopathological evaluation showed normal villous architecture and patchy limited chronic inflammation. The infliximab plasma levels were 26, 24, 17, and 5.3 µg per milliliter before the second, third, fourth, and fifth dose, respectively. The last measured plasma level was available before administration of the sixth dose of infliximab and appeared to be subtherapeutic (0.4 µg per milliliter), after which infliximab treatment was intensified. The infant's weight is shown above the graph, and the standard deviation of weight is shown on the right y axis. TPN denotes total parenteral nutrition.

The results of whole-exome sequencing were negative for a panel of known genetic variants associated with primary immunodeficiency and very-early-onset inflammatory bowel disease, including autoimmune enteropathies such as IPEX (immune dysregulation, polyendocrinopathy, enteropathy, X-linked syndrome), APECED (autoimmune phenomena, polyendocrinopathy, candidiasis, and ectodermal dystrophy), and other IPEX-like autoimmune enteropathies (Ta- ble 1).15,16 IPEX was further ruled out by normal phenotyping of FOXP3 (forkhead box P3) in the blood. The presence of serum antibodies against 75 kDa (harmonin), a finding that is typically specific for autoimmune enteropathy, was observed. However, the role of such antibodies in the pathogenesis of autoimmune enteropathies is uncertain because harmonin autoantibodies may develop secondary to intestinal damage that occurs not only in IPEX but also in other conditions associated with autoimmune enteropathy, including damage caused by the inhibition of co-inhibitory signaling pathways on T cells, as was found in our patient. [15-18]

DIFFERENTIAL DIAGNOSES	TESTS PERFORMED	RESULTS
Step 1. General assessment of the patient with intractable diarrhea		
General investigations in severely ill patients	WBC, electrolytes, liver enzymes and kidney function Ultrasound	Mild thrombocytosis and mild hyponatremia Dilated small intestine loops and thickened small bowel walls
Inflammatory (non-invasive)	Erythrocyte sedimentation rate, C-reactive protein, calprotectin	Normal
Protein-losing enteropathy (PLE)	Albumin, IgG, thyroid function, alpha-1 antitrypsin clearance	Hypoalbuminemia and hypogammaglobulinemia; normal thyroid function, alpha-1 antitrypsine clearance failed
Metabolic	Lipid profile, screening on urine gal-alcohol, basal metabolic investigation	Normal
Gastrointestinal infectious diseases	PCR of viral/bacterial/parasitic gastrointestinal pathogens Blood culture	SARS-CoV-2 molecular PCR positive, all other negative Negative
Cow's milk allergy	Introduction of amino acid-based diet	No difference in clinical condition
Exocrine pancreatic insufficiency	Fecal elastase	Low (NB: in watery secretory diarrhea most likely diluted)
Immunological deficiency	Lymphocyte subset analysis, IgA, IgG, IgM	Hypogammaglobulinemia due to protein-losing enteropathy
Step 2. Findings consistent with protein-losing enteropathy: histopathologic and genetic assessments		
Congenital causes of PLE (e.g. enterocytopathy, inflammatory, immunologic)	Endoscopy with histology	Total villous atrophy and severe active and chronic inflammation
Very early-onset IBD or intractable diarrhea monogenetic causes	Whole-exome sequencing on VEO-IBD panel (including FOXP3, AIRE, IL2RA, STAT5B, LRBA, CTLA4, STAT1, and ITCH)	No mutation
Suspicion of correlation with pembrolizumab exposure on histopathology: advanced immunological assessment		
Autoimmune causes	Anti-enterocyte antibodies, anti-75 kDa (anti-harmonin-antibodies)	Positive antibodies
	Deep immunophenotyping	Highly active CD4+ and CD8+ cells with increased HLA-DR and PD-1 expression
Hypothesis of pembrolizumab-induced immune-related gastroenterocolitis		
Pembrolizumab concentration assays	ELISA on dried blood spot from heel-prick card	38.6 µg/ml mean of two samples (34.7 µg/ml and 41.5 µg/ml)
	ELISA on first available serum (16.5 wk of age)	0.50 ng/ml

Table 1. Differential Diagnoses and Summary of Performed Diagnostics in the Patient. ** ELISA denotes enzyme-linked immunosorbent assay, PCR polymerase chain reaction, SARS-CoV-2 severe acute respiratory syndrome coronavirus 2, and VEO IBD very-early-onset inflammatory bowel disease.*

Finally, immunologic analysis of blood samples revealed that the majority of peripheral CD4+ and CD8+ T cells had a hyperactivated phenotype, as indicated by increased PD-1 and HLA-DR expression (>75% HLA-DR+ [reference value, ≤1% in newborns[19]) (Fig. 2). A similar increase in activated T cells has been observed in adult patients treated with anti–PD-1 therapy. [20] Overall, T-cell activation markers such as HLA-DR and PD-1 serve as surrogate biomarkers for immune-related adverse events and could be related to the observed gastroenterocolitis induced by immune checkpoint inhibitors.

Because the presumed cause of the symptoms was immune-mediated, we initiated 1 week of intravenous prednisolone at a dose of 2 mg per kilogram per day, with subsequent tapering over 13 weeks. During the first week, the diarrhea decreased substantially, and enteral feeding was introduced with the use of an extensive hydrolysate formula with 50% medium-chain triglycerides. A stepwise increase in enteral feeding was

tolerated well, but weight gain seemed to be mostly dependent on parenteral nutrition. After 3 weeks of glucocorticoid administration, duodenal biopsies showed decreases in cellular in-filtrate and apoptosis, whereas villous atrophy remained. Consequently, infliximab was initiated in accordance with treatment guidelines for enterocolitis induced by immune checkpoint inhibitors. [21] This treatment consisted of intravenous administration of infliximab at a dose of 5 mg per kilogram of body weight at 0, 2, and 6 weeks, followed by maintenance treatment at a dose of 5 to 10 mg per kilogram every 4 to 8 weeks on the basis of serum levels of infliximab. Subsequently, enteral feeding was increased and parenteral nutrition decreased over a period of 3 weeks. Prednisolone was tapered and azathioprine was substituted to prevent the development of antibodies against infliximab because of the increased risk of such antibodies in young children during infliximab monotherapy. [22] Vedolizumab could have been used as an alternative treatment, but data were lacking on such therapy in infants. Because of the clinical presentation, we could not rule out the presence of an autoimmune enteropathy without a known genetic mutation at the time of treatment initiation. Thus, we chose this treatment strategy because prolonged treatment was a possible necessity.

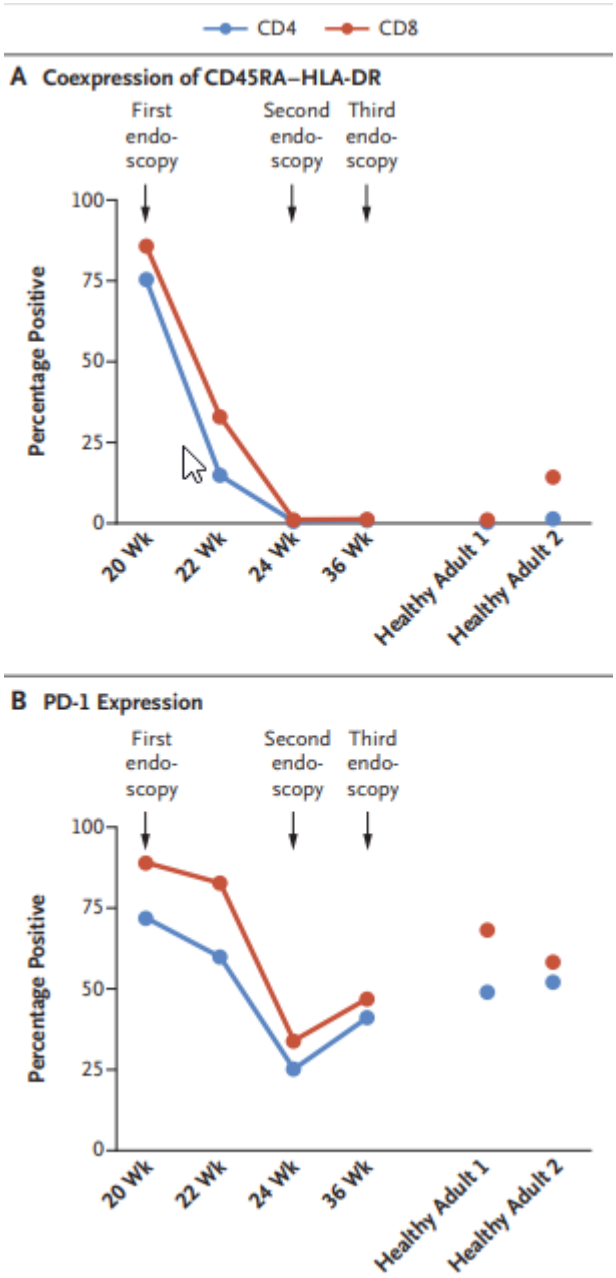


Figure 2. Activated Phenotype Seen in Peripheral T Cells**.** *Shown are the results of flow cytometry of peripheral blood mononuclear cells obtained from the infant at the time of the first endoscopy (20 weeks), at 22 weeks, at the time of the second endoscopy (24 weeks), and at the time of the third endoscopy (36 weeks). Percentages of positivity of biomarkers CD45RA–HLA-DR (Panel A) and programmed cell death protein 1 (PD-1) (Panel B) are shown in CD4+ and CD8+ T cells. Results of analyses in control samples that were obtained from healthy adults are shown at right.*

Ten weeks after admission, the patient was discharged with complete enteral feeding and normal weight gain. After three doses of infliximab, peripheral T-cell activation normalized (Fig. 2) and the mucosa appeared to be normal on gastro-duodenoscopy. Histologic analysis revealed an improving duodenal mucosa with only partial villous atrophy but also ongoing residual chronic and focally active inflammation for which infliximab was continued (Fig. 1 and Fig S1). Gastro-duodenoscopy at 2 years showed nor- mal enteral mucosa, and biopsy revealed normal villous architecture without signs of inflammation. In accordance with other treat- ment regimens for pediatric autoimmune enteropathies, infliximab will be continued until the patient is at least 3 years of age, after which repeated gastro-duodenoscopy will be performed. To further support our

hypothesis that the in utero exposure to pembrolizumab caused the observed gastro-enterocolitis, we developed a new method for determining anti–PD-1 levels on heel-prick cards. A full description of the method is provided in the Supplementary Methods. On enzyme-linked immunosorbent assay of two blood samples obtained by heel prick within 7 days after the infant's birth, the mean pembrolizumab level was 38.6 μg per milliliter (in samples with 34.7 μg and 41.5 μg, respectively). For both assays, an average hematocrit of 40 to 50% was assumed. With an expected maternal Cmax of 148 μg per milliliter of pembrolizumab in plasma 3 weeks before giving birth and a half-life of 22 days, the expected fetal plasma level at birth would have been 75.0 μg per milliliter, which corresponded to a level of 37.5 μg per milliliter in whole blood.[23] The measured heel-prick level was higher than the predicted level, which could be explained by the previously described Fc receptor dependency, resulting in a fetal IgG level that can exceed the maternal level at term.[4,9] Furthermore, a pembrolizumab level of 0.50 ng per milliliter was found in serum obtained from the infant at 4.5 months after birth (≥6 half-lives). Thus, the high level of the drug in the infant's blood supported our diagnosis of pembrolizumab-induced, immune-related gastro-enterocolitis.

DISCUSSION

In summary, we present a case of an infant with severe immune-related gastroenterocolitis after in utero exposure to pembrolizumab. The histo-pathological and immunophenotypic findings — together with the timing and duration of pembrolizumab exposure in utero, the high blood level of pembrolizumab after birth, and the positive response to glucocorticoids and infliximab — all strongly point toward an immune-related gastroenteritis.

This case illustrates the potential of immune checkpoint inhibitors to induce immune-related adverse events in offspring, even several months after birth, and underscores the recommendation that these drugs should be used with great caution during pregnancy.[6] The necessity of initiating treatment during pregnancy, the expected maternal benefit, and gestational age of exposure are variables that need to be taken into account as part of the treatment decision during pregnancy. Although safety information is lacking about the use of the Fc receptor blocker efgartigimod during pregnancy, it has been hypothesized that such treatment could lower the fetal level of immune checkpoint inhibitors and thereby limit the risk of immune-related adverse events in offspring when maternal treatment during the third trimester is considered. However, this hypothesis warrants further investigation to determine the safety of this drug during pregnancy and the efficacy for this indication. When immune checkpoint inhibitors are administered during pregnancy, close monitoring for symptoms in the newborn should be encouraged. Such efforts could lead to early detection and adequate treatment of possible immune- related adverse events, which may develop weeks to months after exposure.[24-27] Finally, our newly developed analysis can be used to measure the antibody levels against PD-1 in dried blood spots. Once we have a better understanding of the at-risk drug level, we can then determine the postnatal risk of immune-related adverse events in such cases.

REFERENCES

1 Khan, S. & Gerber, D. E. Autoimmunity, checkpoint inhibitor therapy and immune-related adverse events: A review. *Semin Cancer Biol* **64**, 93-101 (2020).

2 Zhang, Y. H., Tian, M., Tang, M. X., Liu, Z. Z. & Liao, A. H. Recent Insight into the Role of the PD-1/PD-L1 Pathway in Feto-Maternal Tolerance and Pregnancy. *Am J Reprod Immunol* **74**, 201-208 (2015).

3 Poulet, F. M., Wolf, J. J., Herzyk, D. J. & DeGeorge, J. J. An Evaluation of the Impact of PD-1 Pathway Blockade on Reproductive Safety of Therapeutic PD-1 Inhibitors. *Birth defects research. Part B, Developmental and reproductive toxicology* **107**, 108-119 (2016).

4 Pentsuk, N. & van der Laan, J. W. An interspecies comparison of placental antibody transfer: new insights into developmental toxicity testing of monoclonal antibodies. *Birth defects research. Part B, Developmental and reproductive toxicology* **86**, 328-344 (2009).

5 Anami, Y. *et al.* Malignant melanoma treated with pembrolizumab during pregnancy: A case report and review of the literature. *Mol Clin Oncol* **15**, 242 (2021).

6 Borgers, J. S. W. *et al.* Immunotherapy for cancer treatment during pregnancy. *The Lancet. Oncology* **22**, e550-e561 (2021).

7 Evens, A. M. *et al.* Checkpoint inhibitor immunotherapy during pregnancy for relapsed-refractory Hodgkin lymphoma. *Am J Hematol* (2022).

8 Mittra, A. *et al.* Outcomes of Pregnancy During Immunotherapy Treatment for Cancer: Analysis of Clinical Trials Sponsored by the National Cancer Institute. *The oncologist* **26**, e1883-e1886 (2021).

9 Israel, E. J., Simister, N., Freiberg, E., Caplan, A. & Walker, W. A. Immunoglobulin G binding sites on the human foetal intestine: a possible mechanism for the passive transfer of immunity from mother to infant. *Immunology* **79**, 77-81 (1993).

10 Patil, P. A. & Zhang, X. Pathologic Manifestations of Gastrointestinal and Hepatobiliary Injury in Immune Checkpoint Inhibitor Therapy. *Arch Pathol Lab Med* **145**, 571-582 (2021).

11 Wang, D. Y. *et al.* Clinical characterization of colitis arising from anti-PD-1 based therapy. *Oncoimmunology* **8**, e1524695 (2019).

12 Collins, M. *et al.* Inflammatory gastrointestinal diseases associated with PD-1 blockade antibodies. *Ann Oncol* **28**, 2860-2865 (2017).

13 Irshaid, L., Robert, M. E. & Zhang, X. Immune Checkpoint Inhibitor-Induced Upper Gastrointestinal Tract Inflammation Shows Morphologic Similarities to, but Is Immunologically Distinct From, Helicobacter pylori Gastritis and Celiac Disease. *Arch Pathol Lab Med* **145**, 191-200 (2021).

14 Zhang, M. L. *et al.* Immune-related adverse events in the gastrointestinal tract: diagnostic utility of upper gastrointestinal biopsies. *Histopathology* **76**, 233-243 (2020).

15 Chen, C. B., Tahboub, F., Plesec, T., Kay, M. & Radhakrishnan, K. A Review of Autoimmune Enteropathy and Its Associated Syndromes. *Dig Dis Sci* **65**, 3079-3090 (2020).

16 Singhi, A. D. *et al.* Pediatric autoimmune enteropathy: an entity frequently associated with immunodeficiency disorders. *Mod Pathol* **27**, 543-553 (2014).

17 Walker-Smith, J. A., Unsworth, D. J., Hutchins, P., Phillips, A. D. & Holborow, E. J. Autoantibodies against gut epithelium in child with small-intestinal enteropathy. *Lancet* **1**, 566-567 (1982).

18 Miyazaki, H. *et al.* A case of autoimmune enteropathy with CTLA4 haploinsufficiency. *Intest Res* **20**, 144-149 (2022).

19 van Gent, R. *et al.* Refined characterization and reference values of the pediatric T- and B-cell compartments. *Clin Immunol* **133**, 95-107 (2009).

20 Kim, K. H. *et al.* Immune-related adverse events are clustered into distinct subtypes by T-cell profiling before and early after anti-PD-1 treatment. *Oncoimmunology* **9**, 1722023 (2020).

21 Haanen, J. *et al.* Management of toxicities from immunotherapy: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* **28**, iv119-iv142 (2017).

22 Kansen, H. M. *et al.* Less Anti-infliximab Antibody Formation in Paediatric Crohn Patients on Concomitant Immunomodulators. *J Pediatr Gastroenterol Nutr* **65**, 425-429 (2017).

23 Freshwater, T. *et al.* Evaluation of dosing strategy for pembrolizumab for oncology indications. *J Immunother Cancer* **5**, 43 (2017).

24 Couey, M. A. *et al.* Delayed immune-related events (DIRE) after discontinuation of immunotherapy: diagnostic hazard of autoimmunity at a distance. *J Immunother Cancer* **7**, 165 (2019).

25 Patrinely, J. R., Jr. *et al.* Chronic Immune-Related Adverse Events Following Adjuvant Anti-PD-1 Therapy for High-risk Resected Melanoma. *JAMA Oncol* **7**, 744-748 (2021).

26 Tang, S. Q. *et al.* The Pattern of Time to Onset and Resolution of Immune-Related Adverse Events Caused by Immune Checkpoint Inhibitors in Cancer: A Pooled Analysis of 23 Clinical Trials and 8,436 Patients. *Cancer Res Treat* **53**, 339-354 (2021).

27 Ghisoni, E. *et al.* Late-onset and long-lasting immune-related adverse events from immune checkpoint-inhibitors: An overlooked aspect in immunotherapy. *Eur J Cancer* **149**, 153-164 (2021).

Chapter 12 Proton therapy of a pregnant patient with nasopharyngeal carcinoma – a case-report

Joosje Heimovaara*, Jeroen Blommaert*, Jeffrey Free, René Bolt, Elske Gort, Tom Depuydt, Cristina Boso Martinez, Mirthe Schoots, Mathilde van Gerwen, Marry van den Heuvel-Eibrink, Johannes Langendijk, Caorlien Schröder, Frédéric Amant, Sanne Gordijn, Edwin Oldehinkel

Clinical and Translational Radiation Oncology, May 2022
* Contributed equally to the manuscript

ABSTRACT

Background and purpose Radiotherapy during pregnancy is rarely administered due to lack of data and practical challenges. This is the first detailed report of proton therapy as cancer treatment for a pregnant patient with nasopharyngeal carcinoma.

Materials and methods Pencil beam scanning proton therapy was prescribed to a pregnant patient to a total dose of 70 Gy (RBE) to the therapeutic CTV and 54.25 Gy to the prophylactic CTV, delivered in 35 fractions with a simultaneous integrated boost technique.

Results Phantom measurements showed a thirty-fold decrease in fetal radiation dose when using proton compared to photon therapy, with a total fetal dose of 5.5 mSv for the complete proton treatment, compared to 185 and 298 mSv for the photon treatment with and without lead shielding, respectively. After administering proton therapy during pregnancy, at 39 weeks of gestation a healthy boy with a birthweight on the 83th percentile was delivered. Pediatric follow-up at 2 months of age of the offspring showed normal growth and age-adequate motor development with no signs of neurological problems. MR follow-up of the tumor 3 months after the end of treatment showed complete remission.

Conclusion This case demonstrates the potential of proton therapy for treatment during pregnancy. Compared to photon therapy, proton therapy can significantly limit fetal dose, while simultaneously offering a more optimized treatment to the patient.

INTRODUCTION

Cancer complicates about 1 in 1000 to 2000 pregnancies. [1] With growing evidence regarding the safety of cancer treatment during pregnancy, approximately 69% of pregnant patients are currently treated with surgery or cytotoxic modalities. [2] However, only 1-3% of pregnant cancer patients receive radiotherapeutic treatment.[2,3] Although guidelines indicate that this is safe when the fetal dose is kept below 100 mSv, radiation oncologists are hesitant to treat during pregnancy due to practical challenges and lack of data.[2-5]

Pencil beam scanning intensity modulated proton therapy (IMPT) has recently provided new opportunities for radiotherapy during pregnancy. So far, three pioneering case studies have reported on the feasibility of IMPT during pregnancy.[6-8] However, these studies did not compare the fetal radiation dose with state-of-the-art photon therapy and scarcely discussed the oncological and obstetrical outcomes. One Monte Carlo simulation study comparing simulated (phantom) fetal dose during photon therapy with IMPT for a brain tumor showed a ten-fold reduction in fetal radiation dose.[9] This study was performed using an artificial tumor and patient model and was not validated by physical measurements.

In this study we describe the outcomes of a pregnant woman receiving IMPT for a nasopharyngeal carcinoma, and the outcomes of her child, and calculated the fetal radiation doses during proton and photon therapy using phantom measurements.

CASE

A 33-year-old Asian pregnant woman, gravida 4, para 1, 24 weeks of gestation with no relevant medical history and normal glucose tolerance test, presented with a two-month history of frequent epistaxis, nasal obstruction and palpable mass in the neck. Naso-endoscopy showed an exophytic mass located in the right nasopharynx and biopsy confirmed non-keratinizing squamous cell carcinoma, Epstein-Barr virus (EBV) positive. Head and neck magnetic resonance imaging (MRI) showed a lesion in the right nasopharynx (approximately 26x32x30 mm), extending over the midline to the left side. There were bilateral retropharyngeal pathological lymph nodes as well as in the right neck, level II, III and V, with a maximal short axis diameter of 20 mm. Computer tomography (CT) of the thorax did not show distant metastases. Definitive staging was a cT1N1M0 (according to TNM 8th edition) EBV+ nasopharyngeal carcinoma.[10] The patient was referred to an academic medical hospital with a proton facility and experience in the field of cancer and pregnancy, where radiotherapy with IMPT was indicated after multidisciplinary consultation.

The patient was immobilized using a 5-point thermoplastic mask and underwent a non-contrast enhanced planning CT and MRI. Gross tumor volume contained the primary tumor and pathological lymph nodes. Clinical target volume (CTV) was obtained by adding a 5-mm margin in all directions adjusted to anatomical structures for the therapeutic CTV and a 10-mm margin for the prophylactic (elective) CTV. The prophylactic CTV also included lymph node levels II, III, IVa, Vab and VIIa according to consensus guidelines.[11] Prescribed radiation dose was 70 Gy (RBE) delivered in 35 fractions of 2 Gy to the therapeutic CTV and 54.25 Gy (RBE)

in 35 fractions of 1.55 Gy to the prophylactic CTV using a simultaneous integrated boost technique and CTV-based robust treatment planning.

	PROTON	PHOTON
TREATMENT SYSTEM	IBA Proteus Plus	Varian Truebeam STX
TECHNIQUE	Pencil beam scanning	6 MV VMAT
TPS	Raystation v9A	Eclipse v16.1
COUCH ROTATION	0°	10°
GANTRY ROTATION	50, 85, 160, 200, 280 and 315°	90 to 280° back-and-forth
RANGE SHIFTER (4CM WET)	50, 85, 280 and 315°	NA
MONITOR UNITS	1792.37 MU	373 MU
LEAD SHIELDING	None	7.7 cm frontal and 5 cm left
DETECTOR FOR FETAL DOSIMETRY	FHT 762 Wendi-2	TLD-100 chipstrate
ESTIMATED FETAL DOSE	5.5 mSv	185 mSv

Table 1 Treatment parameters for the proton and photon plans.

Before starting IMPT, fetal radiation dose was compared between proton and photon therapy plans (Table 1, Figure 1) using phantom measurements. The palpable distance between fetus and edge of the CTV before start of treatment was 30 cm. Accounting for dose uncertainties and fetal growth during treatment, fetal radiation dose was measured at 20 cm from the caudal border of the CTV. The same phantom set-up (Figures 2 and 3) was used for fetal radiation dose estimation in both proton and photon plans, consisting of a CIRS proton therapy head phantom (model 731-HN) and RW3 solid water plates for thorax and abdomen. For the proton plan. fetal dose was estimated using the FHT 762 *Wendi-2* detector, placed with its center at 20cm from the caudal border of the CTV using a vertical stack of 30 by 30 cm solid water plates. The Wendi-2 detector is designed to measure H*(10) for neutrons up to 5 GeV as well as gamma radiation. For the VMAT photon plan, TLD-100 chipstrate detectors were used to estimate the fetal radiation dose, placed in a 16cm horizontal stack of 40 by 40 cm solid water plates at a depth of 7 cm and at 20cm from the caudal border of the CTV. The TLD' s were calibrated in absorbed dose against an FC65-G Scanditronix-Wellhöfer Farmer-type ionisation chamber in a stack of solid water plates, using a 6MV beam and a 10 by 10cm field at a depth of 10cm and an SSD of 90 cm.

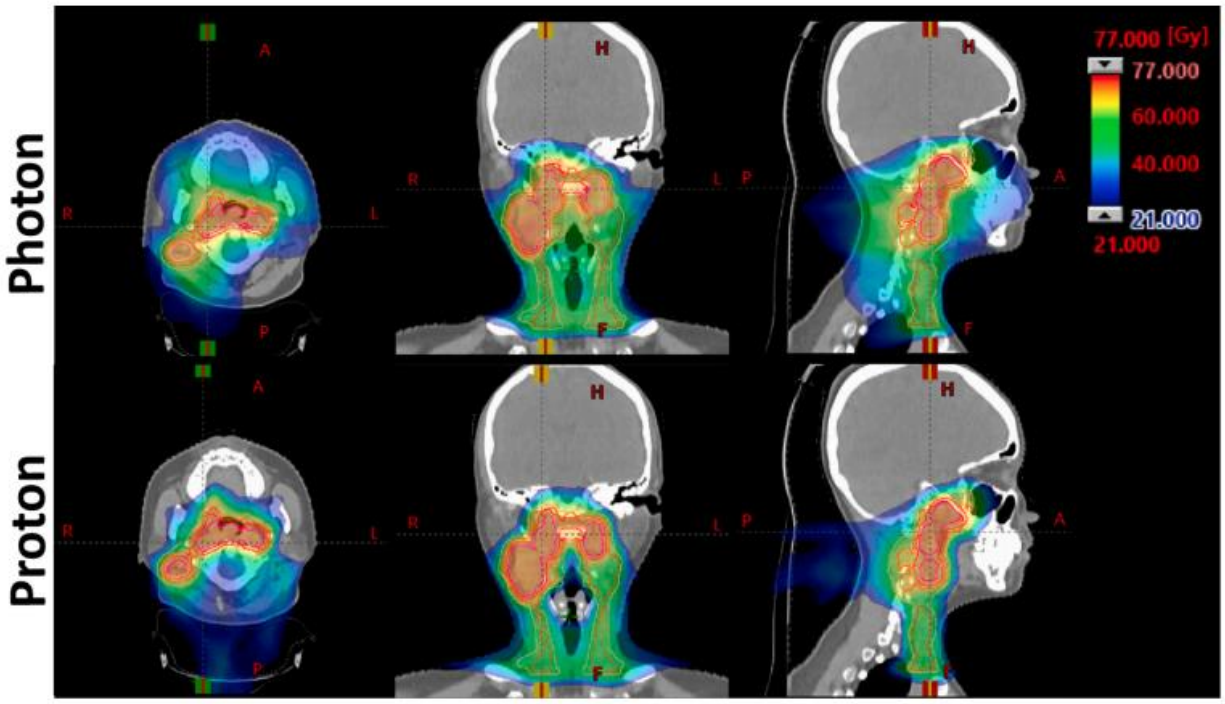


Figure 1. Proton and photon treatment plans. The top three panels show an axial, coronal and sagittal plan of the VMAT photon plan. The lower three panels show the same planes for the IMPT plan.

A Pencil Beam Scanning (PBS) IMPT plan was made using the Raystation 9A treatment planning system (RaySearch Laboratories, Sweden) for an IBA Proteus Plus (IBA, Belgium) delivery system. The plan setup was performed according to clinical routine due to the lack of specific guidelines for treatment of pregnant women. The proton plan consisted of 6 beams without couch rotations and gantry angles of 50, 85, 160, 200, 280 and 315° with a total of 1792.37 MU. Beams at gantry angle 50, 85, 280 and 315° were equipped with a range shifter of 4cm water equivalent thicknessWET. The treatment plan was robustly optimized using the RayStation Monte Carlo dose engine with an uncertainty of 1.0%, an isotropic setup uncertainty of 3.0 mm and a range uncertainty of ±3.0%. The final plan was evaluated on CTV coverage based on the voxel-wise minimum and voxel-wise maximum dose maps constructed out of the 28 scenarios (i.e. 14 isotropic setup scenarios with maximum setup uncertainty of 3.0 mm for two (±3.0%) range uncertainty scenarios).[12] The 6 MV VMAT photon plan was created (Eclipse v16.1, Varian, USA) for a Varian Truebeam STX using a PTV with 3mm margin around the CTV, according to clinical routine. The plan consisted of a back-and-forth arc of 90 and 290° at 10° table rotation, to avoid irradiating from angles where lead shielding was impossible. In line with AAPM guidelines, monitor units were limited to 373 MU and frontal 7,7cm and left 5cm thick abdominal lead shielding was used.[13] Phantom measurements showed an estimated total fetal radiation dose of 5.5 mSv for the proton treatment, of which 4.6mSv due to neutrons. For photon treatment the estimated total fetal doses were 185 and 298 mSv, respectively with and without lead shielding.

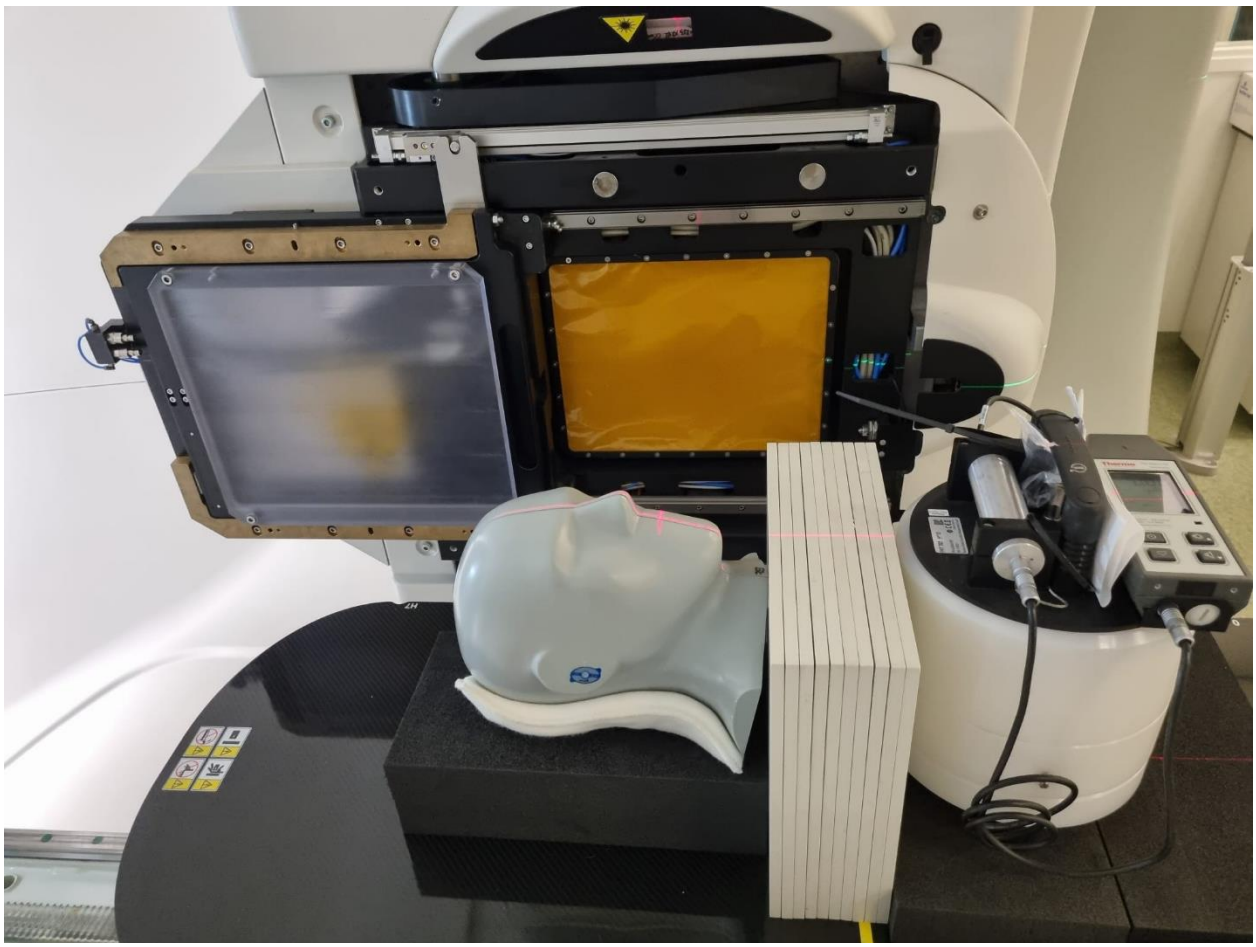


Figure 2. Phantom set-up for fetal dose estimation during proton treatment.



Figure 3. Phantom set-up for fetal dose estimation during the VMAT photon treatment.

IMPT started at 27 weeks of gestation. The patient underwent daily orthogonal kilovoltage X-ray imaging and cone beam CT during treatment to ensure correct patient setup each day, attributing to an additional fetal dose of 0.08 mSv (2.25 µSv per fraction) as measured by the Wendi-2 detector. Additionally, the patient received weekly repeat CTs to verify adequate dose coverage and dose to organs at risk. Plan adaptations were not required. The weekly repeat and planning CTs accounted for an additional fetal radiation dose of

0.21mSv, with no abdominal shielding being used. [14] Accounting for both treatment and imaging, the total fetal radiation dose was 5.8 mSv.

The course of pregnancy from an obstetric perspective was uneventful, with fetal growth along the 70th percentile and normal umbilical artery Dopplers. During treatment, patient developed grade 2 mucositis and grade 3 dermatitis (according to the Common Terminology Criteria for Adverse Events version 4.0 (CTCAE 4.0) for which additional symptomatic pain relief was started at 29 weeks of gestation.[15] Lidocain spray 10% 3 times a day and additional tramadol 50mg two times a day resulted in efficient pain relief. Six weeks after the last fraction, symptoms were completely resolved.

At 39 weeks of gestation, four months after diagnosis and eight weeks after end of treatment, the patient gave birth to a healthy boy after spontaneous delivery. The boy weighted 3820 grams (83th percentile) and measured 53 cm in length and 36 cm in head circumference.[16] APGAR scores were 9 and 10 at respectively 1 and 5 minutes. No congenital or neurological abnormalities were observed in the child. The placental weight was 445 gram (normal for gestational age) and general pathological examination showed no abnormalities. Microscopic placental examination according to the Amsterdam criteria showed more than 45 avascular villi, compatible with the diagnosis of a high-grade fetal vascular malperfusion (FVM).[17] No maternal vascular malperfusion, chronic villitis or chronic intervillositis were found. The maturation of the parenchyma was slightly immature for the given gestational age.

Follow-up at two months of age showed normal general health, development and growth of the boy. No signs of neurological problems were observed. Long-term follow-up of this boy is planned to evaluate possible long-term side effects. Three months after treatment, the patient underwent an MRI of the head and neck which showed a complete remission. Six months after treatment no clinical signs of recurrent disease were observed.

DISCUSSION

Here we present the potential of IMPT for treatment during pregnancy and show a significantly reduced fetal radiation exposure during IMPT compared to photon therapy, while simultaneously offering a more conformal treatment to the patient.

The FVM found in the placenta is a common lesion related to fetal growth restriction and adverse perinatal outcomes, however the abnormalities of FVM are also described in uneventful pregnancies with normal outcome. [18] Fetal growth restriction did not occur in our case as the birthweight was at the 83rd percentile after intrauterine growth along the 70th percentile during pregnancy. FVM can be caused by damage to or compression of fetal vessels. [17,19,20] No direct explanation for the avascular fetal villi was found. Although it has been suggested that irradiation can cause maternal vascular malperfusion (MVM), no signs of MVM were observed. Whether irradiation causes direct damage to the villous vasculature is yet unclear.[21] In vitro and

animal studies need to be conducted to investigate the plausible pathophysiological mechanisms of fetal radiation on FVM.

The fetal radiation dose during proton therapy was observed to be dominated by secondary neutrons, accounting for 84% of the dose, which cannot be properly shielded using lead. Moreover, as PBS does not use collimation to shape the beam, leading to less head scatter can be expected and therefore less need for abdominal shielding. This in contrast to photon treatment, where we observed a 38% reduction in fetal dose when applying lead shielding. Next to that, we minimized the fetal dose during photon treatment by limiting the treatment angles and MU. These modifications of the photon treatments provide additional practical challenges for treatment planning and execution, which was not the case for proton therapy.

Currently, the implementation of proton therapy during pregnancy faces several hurdles. First, neutron dominated out-field radiation generates uncertainties on the placental and fetal radiation dose and necessitate the use of large detector volumes. This can be solved by using more advanced smaller-sized detectors, which in turn allow for more realistic phantom geometries. Alternative, validated computational models could offer adaptable and patient-specific computation of fetal doses. Second, there is a lack of data on placental development and function, as well as on long-term outcomes in children born after radiotherapy during pregnancy. Clinicians should therefore be encouraged to report known cases and register pregnant patients receiving proton therapy in national and international registries. Third, in contrast to photon therapy, guidelines on the use of proton therapy during pregnancy are still to be established.[22] In conclusion, future research should improve the accuracy of the fetal neutron dose estimation during proton therapy, leading to practical guidelines and standardization on the use of proton therapy during pregnancy.

REFERENCES

1 Stensheim, H., Møller, B., Van Dijk, T. & D., F. S. Cause-specific survival for women diagnosed with cancer during pregnancy or lactation: A registry-based cohort study. *Journal of Clinical Oncology* **27**, 45-51 (2009).

2 de Haan, J. *et al.* Oncological management and obstetric and neonatal outcomes for women diagnosed with cancer during pregnancy: a 20-year international cohort study of 1170 patients. *The Lancet Oncology* **19**, 337-346 (2018).

3 Maggen, C. *et al.* Pregnancy and Cancer: the INCIP Project. *Current Oncology Reports* **22** (2020).

4 Kal, H. B. & Struikmans, H. Radiotherapy during pregnancy: fact and fiction. *The Lancet. Oncology* **6**, 328-333 (2005).

5 Mazzola, R. *et al.* Modern radiotherapy in cancer treatment during pregnancy. *Critical reviews in oncology/hematology* **136**, 13-19 (2019).

6 le Guevelou, J. *et al.* [Measurement of out-of-field dose to the uterus during proton therapy of the head and neck]. *Cancer Radiother* **24**, 138-142 (2020).

7 Kalbasi, A. *et al.* Proton craniospinal irradiation during the third trimester of pregnancy. *Pract Radiat Oncol* **8**, 213-216 (2018).

8 Wang, X. *et al.* Spot scanning proton therapy minimizes neutron dose in the setting of radiation therapy administered during pregnancy. *J Appl Clin Med Phys* **17**, 366-376 (2016).

9 Geng, C. *et al.* Dose assessment for the fetus considering scattered and secondary radiation from photon and proton therapy when treating a brain tumor of the mother. *Phys Med Biol* **61**, 683-695 (2016).

10 Brierley, J. D., Gospodarowicz, M. K. & Wittekind, C. *TNM classification of malignant tumours*. (John Wiley & Sons, 2017).

11 Grégoire, V. *et al.* Delineation of the neck node levels for head and neck tumors: a 2013 update. DAHANCA, EORTC, HKNPCSG, NCIC CTG, NCRI, RTOG, TROG consensus guidelines. *Radiother Oncol* **110**, 172-181 (2014).
12 Korevaar, E. W. *et al.* Practical robustness evaluation in radiotherapy - A photon and proton-proof alternative to PTV-based plan evaluation. *Radiother Oncol* **141**, 267-274 (2019).
13 Stovall, M. *et al.* Fetal dose from radiotherapy with photon beams: report of AAPM Radiation Therapy Committee Task Group No. 36. *Med Phys* **22**, 63-82 (1995).
14 Saltybaeva, N. *et al.* Radiation Dose to the Fetus From Computed Tomography of Pregnant Patients-Development and Validation of a Web-Based Tool. *Invest Radiol* **55**, 762-768 (2020).
15 *CTCAE 4.03. Common Terminology Criteria for Adverse Events (CTCAE). Version 4.0. Published: May 28, 2009 (v4.03: June 14, 2010).* https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/ctcae_4_with_lay_terms.pdf (accessed Jan 2022)
16 Hoftiezer, L. *et al.* From population reference to national standard: new and improved birthweight charts. *Am J Obstet Gynecol* **220**, 383.e381-383.e317 (2019).
17 Khong, T. Y. *et al.* Sampling and Definitions of Placental Lesions: Amsterdam Placental Workshop Group Consensus Statement. *Arch Pathol Lab Med* **140**, 698-713 (2016).
18 Pathak, S., Lees, C. C., Hackett, G., Jessop, F. & Sebire, N. J. Frequency and clinical significance of placental histological lesions in an unselected population at or near term. *Virchows Arch* **459**, 565-572 (2011).
19 Kraus, F. T. & Acheen, V. I. Fetal thrombotic vasculopathy in the placenta: cerebral thrombi and infarcts, coagulopathies, and cerebral palsy. *Hum Pathol* **30**, 759-769 (1999).
20 Schoots, M. H., Gordijn, S. J., Scherjon, S. A., van Goor, H. & Hillebrands, J. L. Oxidative stress in placental pathology. *Placenta* **69**, 153-161 (2018).
21 Wolters, V. *et al.* Placental pathology in cancer during pregnancy and after cancer treatment exposure. *Placenta* **111**, 33-46 (2021).
22 ICRP. Pregnancy and medical radiation. *Annals of the ICRP* **84**, 1-43 (2000).

Part IV General discussion and conclusion

A decade after the official start of the International Network on Cancer, Infertility and Pregnancy (INCIP), and over twice as long since the initial publications on the utilization of chemotherapy during pregnancy, a substantial amount of knowledge has become available on the management of cancer in pregnancy. Despite this, translating the obtained knowledge into daily practice, particularly in the context of specific tumor types at varying stages of disease and gestational age, remains challenging and requires a high degree of expertise.

This thesis demonstrates the impact of the establishment of the Advisory Board on Cancer, Infertility and Pregnancy (ABCIP, Figure 1), where the latest evidence is combined with consensus for patient-specific situations. The research conducted in this thesis provides an overview of the foundation of the ABCIP (**Part II**) and identifies and investigates the gaps in knowledge based on real-world questions received by the board (**Part III**). **Part II** emphasizes the importance of pooling expertise to improve the care of pregnant cancer patients. Based on the results of an international survey (**Chapter 4**) and the description of ten years of experience of the Dutch national MDAB for cancer in pregnancy (**Chapter 5**), the foundation of the **ACBIP** is described in **Chapter 6**. In **Part III**, recent clinical challenges encountered when managing cancer during pregnancy are explored, focusing on the complexity of balancing maternal and fetal health. It underscores the diverse spectrum of cancer types and (novel) treatment modalities, each presenting unique risks and outcomes. It addresses the critical need for individualized care, particularly in cases of rare and aggressive malignancies where evidence is limited.



Figure 1 Logo of the ABCIP

THE WAY TO ABCIP

Levels of evidence: from case reports to large cohort studies

Much of the research presented in this thesis is based on first-in-literature cases, case series, or relatively small cohort studies. These studies contribute to the existing literature on cancer during pregnancy, a field that is inherently limited by small sample sizes due to the rarity of the simultaneous occurrence of cancer and pregnancy. Even though the largest studies on cancer in pregnancy published to date are still retrospective cohort studies, often without a control group, these studies have significantly advanced our understanding of cancer in pregnancy, and serve the basis for existing clinical care guidelines for this group of patients. Large population-based cohort studies in Scandinavia combined data from the Cancer Registry and the Birth Registry. They told us more about the incidence of cancer in pregnancy, and showed for example that cancer during pregnancy does not increase the risk of cause-specific death.[1] By registering pregnant women with cancer in

their cohort study and including control patients, the INCIP tried to increase the level of evidence by increasing the sample size of their studies. For example, De Haan et al included 1,170 pregnant cancer patients from a variety of cancer types and reported on oncological and obstetric outcomes.[2] Van Gerwen et al. included 755 pregnant women with cancer treated with chemotherapy in their paper to draw conclusions on its safety during pregnancy for the children.[3] Lastly, Amant et al compared 662 pregnant breast cancer patients to 2081 non-pregnant controls.[4] The time necessary to obtain these cohort sizes underscore the ongoing challenges of conducting research in this rare and complex population. It also shows that these cohorts are essential to improve care as clinical trials in pregnant women are not ethically or practically feasible.

Case reports sit at the lower end of the EBM pyramid. However, their value lies in their ability to generate hypotheses for future research. By documenting specific clinical events, they pave the way for further review, the gathering of case series, and ultimately provide a foundation for the design of studies higher in the pyramid. In the field of cancer in pregnancy, case reports, such as those described in **Chapter 11 and 12,** have a signalling function. For example, the first online available case reports documenting the use of chemotherapy during pregnancy date back to the 1960s.[5] A case report published in 1964 described a child with multiple congenital anomalies born after exposure to cyclophosphamide during the first trimester of pregnancy. [5] In contrast, case reports published in the 80s were mostly with reassuring outcomes for the child.[6-8] These reports, based on single cases, concluded that chemotherapy could be safely administered during the third trimester, and likely also in the second trimester. A few years later, case series began to appear, reporting on women receiving chemotherapy in the first trimester, without short term or long term consequences for the children.[9] This led to the initial suggestion that treating pregnant women using protocols designed for non-pregnant patients would be safe throughout pregnancy.

Later, more reports highlighted cases of congenital malformations in children exposed to chemotherapy in utero, particularly when treatment was administered in the first trimester of pregnancy.[10,11] Today, it is well-established that chemotherapy can be harmful if given before 12 weeks of gestation. The study by Van Gerwen et al., which included 775 pregnant women who received chemotherapy between 1977 and 2019, provided statistically significant evidence that chemotherapy administered before 12 weeks of gestation increased the risk of congenital malformations.[3] This reinforces the importance of description of cases with both positive and negative outcomes, next to the necessity of larger sample sizes to draw reliable conclusions. It also underscores the need for caution when interpreting findings from case reports or case series. Larger cohort studies are necessary to validate early observations as seen in case reports, and guide clinical practice.

Clinical care when evidence is low – the idea of mindlines

Chapters 1 and 2 of this thesis conclude that although the knowledge of cancer in pregnancy is increasing, providing the most appropriate care for pregnant women with cancer continues to present a significant chal-

lenge. A questionnaire distributed to physicians worldwide, as detailed in **Chapter 4**, revealed that the frequency of clinical exposure of health care professionals to pregnant women with cancer is relatively low, and that expert consultation is commonly requested. As stated before, level 1 evidence is not possible for this group of patients, and level 2 evidence will also be minimally available. Therefore, treatment decisions are mostly relying on experience, skill and judgement. This way of decision making is not unique for cancer in pregnancy.

In a study investigating how primary care clinicians derived their individual and collective healthcare decisions, Gabbay and Le May were the first to introduce the principle of 'mindlines' in 2004.[12] They concluded that clinicians rarely accessed explicit scientific evidence but relied on mindlines (Figure 2) – collectively reinforced, internalized, tactic guidelines. These were based on a combination of brief reading and their own experiences and those of their colleagues. The knowledge of mindlines was mentioned to be 'self-organising' and achieves stability over time. When Lander et al looked at the forms of evidence used for decision making in two internal medicine teams in two teaching hospitals in 2019, they also observed that these mindlines played a critical role in medical decisions.[13] Clinicians combined formal evidence with contextual factors like experience, peer interaction and patient context. Next to that, they found out that the used form of evidence varies per role of the team member. Senior clinicians tended to invoke mindlines formed through experience and peer-reviewed articles, whereas trainees mainly used summaries and online tools such as Up-to-Date.

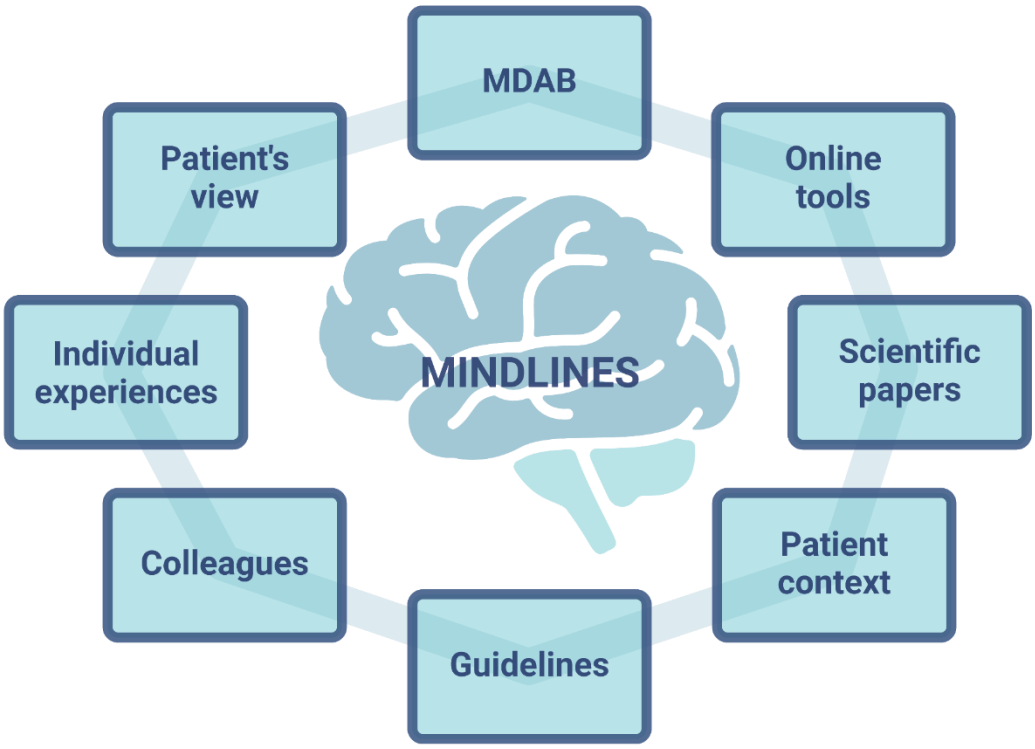


Figure 2. An overview of the aspect 'mindlines' *Figure created in BioRender.com*

Advisory boards for tailor made care for each patient

Advisory boards use a combination of EBM and mindlines, as they combined scientific knowledge and personal expertise. By using advisory boards, the knowledge of the board increases, leading to more stable and conclusive recommendations over time. There are different ways to organize MDABs. Besides the standard oncologic local, regional or even national tumour boards discussing patients in physical meetings, there are nowadays many digital national and international tumour boards. The biggest difference between all these tumour boards and ABCIP is that these tumour boards have a fixed time to discuss patient, whereas ABCIP by its logistics is not depending on this fixed time.

Prior to the launch of the ABCIP, initiatives such as the European Reference Networks (ERNs) already tried to tackle complex or rare diseases that require highly specialized treatment and a concentration of knowledge and resources.[14,15] Most ERNs virtually discuss cases a few times a month through their Clinical Patient Management System (CPMS).[16] This online platform, which is secure and encrypted, is designed to facilitate the gathering of pertinent case information and to enable free-flowing discussion among experts within the specific ERN. However, the consultations are virtual meetings, during which only a limited number of cases can be discussed within a specified time frame. In order for members to participate in the discussion of these

cases, they must attend the meeting at the designated time and do not have time to think about the suggestions of their colleagues before answering. White et al. describe in their critical evaluation of the ERN on Rare Endocrine Conditions that physicians using the platform encounter technical difficulties. [17] Additionally, they showed a decline in active members in the virtual consultations over time since the start of the project.

The ABCIP: discussing cancer in pregnancy cases without time or border constraints

To address this issue of doctors' limited free time and to avoid a decline in active members, ABCIP developed a solution that allowed them to log on to the platform at their convenience to discuss incoming cases. As the Dutch MDAB discussed their cases by email and the ERNs had a website where they could track the cases they wanted to discuss virtually, we tried to combine the two for optimal discussion of incoming cases. At the beginning of this doctoral project in 2020, we first looked for a web developer to help us develop a secure, GDPR-compliant website, taking into account all aspects of the ABCIP's working methods, as we described in **Chapter 6** (Figure 3). Together with this web developer, we designed a workflow, included different languages for all national ABCIP boards to discuss cases in their own language, and kept the website up to date.

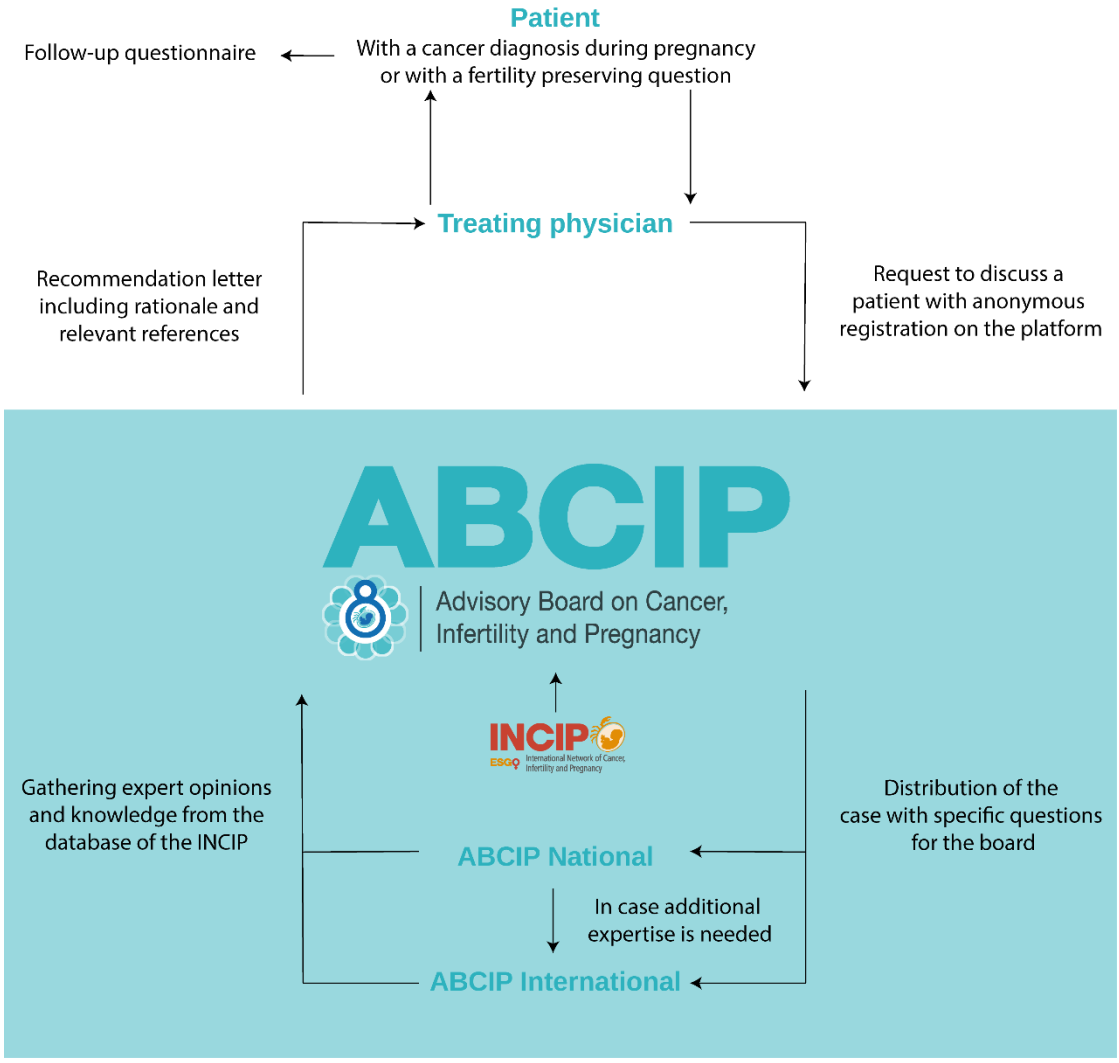


Figure 3. Overview of the working methods of the ABCIP. Physicians treating a patient with a cancer diagnosis during pregnancy or a patient with a fertility preserving question can anonymously register their cases on the ABCIP platform by filling in a format with: 1) oncological diagnostic information; 2) patients desire to preserve the pregnancy or not; 3) proposed treatment for their patient (in

non-pregnant setting) and 4) a specific question for the board. The case is then distributed to the specific advisory board to discuss on a secured forum. All expert opinions and additional knowledge from the database of the INCIP are gathered and the board composes a recommendation letter including rationale and relevant references that, after approval of the whole advisory board, is sent back to the requesting physician within 4-7 days after submitting the request.

The first case discussed on the platform was received on May 18th 2021 (Figure 4). After starting with the already existing Dutch MDAB and the International and Belgian ABCIP, ABCIP Denmark discussed its first case in August 2023, and ABCIP Italy and Spain-Iberoamerica in September 2023. ABCIP Poland will start operating on our platform at the end of this year.

As of September 18th 2024, exactly three years after its first case was being discussed, the ABCIP had already addressed 386 requests for advice from 44 countries. Over the last year, approximately 3 cases have been discussed per week. Nowadays, six separate advisory boards (being International, The Netherlands, Belgium, Spain-Iberoamerica, Italy and Denmark) operate individually on the platform. An overarching general board was appointed, consisting of medical specialists of most countries operating on the platform. Twice-yearly, board meetings are being held to discuss the working methods, keep everyone up-to-date and discuss newly available knowledge within the cancer in pregnancy field.

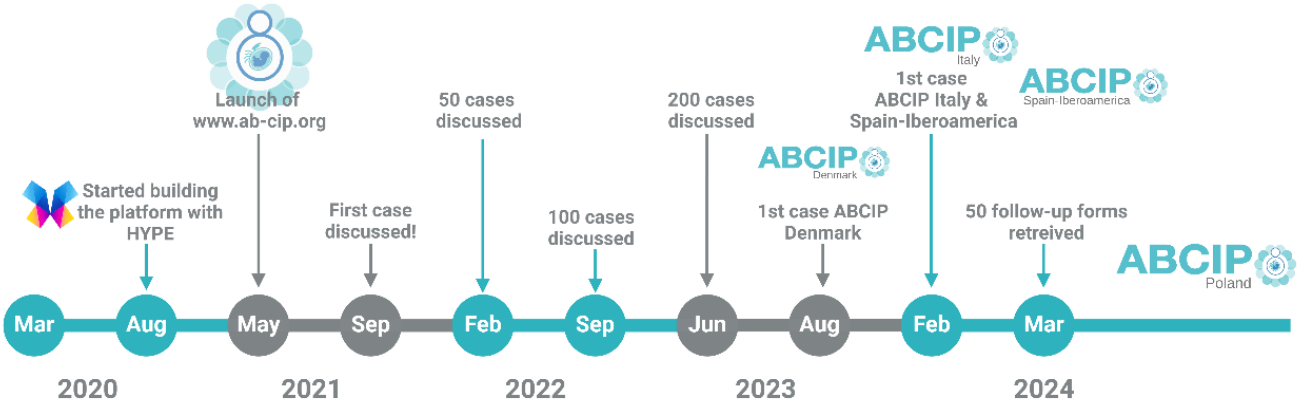


Figure 4. Timeline of the foundation of the ABCIP. *Figure created in BioRender.com*

A major difference from 'normal' MDABs is that the ABCIP is made up of a variety of medical disciplines that do not normally work together. Tumour boards are used to discussing cases in a completely different way to, say, obstetricians and paediatricians. Discussing these cases together takes doctors out of their comfort zone.

It is important to be clear about the boundaries of such initiatives. From the outset, the role of the ABCIP has been to support clinicians without interfering with the actual care of patients. In particular, the ABCIP does not offer direct patient advice or act as a formal second opinion, and there is no therapeutic relationship between the board and the cases discussed. Instead, the board acts as an advisory body to physicians and supports the development of mindlines in both treating and recommending physicians.

Future perspectives on the ABCIP

The online ABCIP platform provides rapid and reliable guidance to healthcare professionals across the globe. This platform not only enhances the speed and accessibility of expert consultation but also opens new possibilities for the future of international, collaborative healthcare. By centralizing expertise and providing a global reach, this model has the potential to significantly improve outcomes, especially for rare or complex cases where local expertise is limited. The structure and success of ABCIP could serve as a model for similar initiatives addressing other complex tumour types, rare diseases, and special patient populations.

In order to make the expertise of the ABCIP available to all physicians in need of recommendations, the ABCIP should be recognised as an official body by national governments, health authorities or hospitals. In this way, the ABCIP or similar initiatives should be able to receive funding to keep the website up to date and to keep doctors in charge of organising the platform.

While the establishment of the ABCIP represents a significant advancement in the care of pregnant women with cancer, increasing knowledge obtained by discussing cases on this platform, and using follow-up information to improve recommendations will be crucial. Next to that, investigating the requests, recommendations and follow-up information will not only validate the efficacy but also help identify areas where further improvements and research are needed. In the future, analysis of these cases and the follow-up data will show us the specific effects of using an international (online) MDAB for pregnant women with cancer. As the field of cancer research continues to evolve, the ABCIP will play a pivotal role in ensuring that pregnant women with cancer receive the highest standard of care, tailored to their specific needs.

EXPANDING FUTURE KNOWLEDGE ON CANCER IN PREGNANCY

Till now, the main message of cancer in pregnancy related research has been that there are treatment options during pregnancy with acceptable fetal toxicity and overall good outcomes of the mothers. But by discussing almost 400 cases on the ABCIP platform, we can conclude that this is not always the case. The ABCIP does more than just facilitate decision-making in challenging cases; it also highlights gaps in existing knowledge. As noted in **Chapters 2 and 4**, there is a significant lack of evidence-based literature in the field of cancer and pregnancy. Beyond simply providing a platform for informed decision-making in the absence of robust guidelines, this thesis demonstrates that the process is reciprocal: through the utilization of the ABCIP, new knowledge gaps are identified, which can then drive further scientific inquiry, as shown in **Part III**.

Following requests for advice from mothers with a very poor prognosis during pregnancy and the risk of maternal death during pregnancy, we studied the group of women with maternal death related to cancer in pregnancy (**Chapter 7**). In the absence of information on sarcomas diagnosed during pregnancy, we examined all cases of sarcomas diagnosed during pregnancy registered in INCIP and published in the literature in **Chapter 8**. Using the expertise of the INCIP and bringing together experts working in the ABCIP, we carried out a comprehensive review of the literature on the use of immunotherapy to treat cancer during pregnancy (**Chapter 10**). With all the new knowledge gathered during these years and by **Chapter 10**, we assembled a group

of experts in the field and developed consensus-based guidelines for haematological malignancies in pregnancy (**Chapter 9**).

Improving care by making good use of case reports

As previously mentioned, pregnant women are excluded from clinical trials. All available information on the use of for example novel treatment modalities in pregnancy is based on case reports, as we exemplified by **Chapter 11 and 12**. **Chapter 11** described the first case of an immune-related adverse event in a child due to in utero exposure to pembrolizumab. **Chapter 12** shows the possibilities of proton therapy during pregnancy and the decreased fetal radiation exposure compared to conventional photon therapy. Expansion of the available data in the field of cancer in pregnancy would ensure that both oncological and obstetrical care continue to evolve in parallel with advancements in cancer treatment and obstetrical care.

While case reports occupy a lower tier in the EBM pyramid, their importance in documenting novel observations or rare outcomes cannot be ignored. To improve the quality of research on cancer in pregnancy, data from larger numbers of published case reports could be combined in the future to create larger case series to allow retrospective analyses, as we tried to do in **Chapter 8** of this thesis. Unfortunately, there is a lack of validated formats to write or score case reports. The same lack of validated quality assessment existed when **Chapters 11 and 12** were published**.** Combining case reports necessitates uniform and complete information and warrants high quality of the case description. The development of validated quality checks for case reports is an essential aspect for future research. For rare situations as cancer and pregnancy, systematic reviews based on published high quality cases will lead to larger sample sizes and more reliable datasets.

Current formats, such as those proposed by the Joanna Briggs Institute (JBI) [18] which we used when checking the case reports for **Chapter 8**, provide a structured approach to writing and reviewing case reports, but these frameworks lack formal validation. The next step would be to adapt such formats specifically for our patient population. This would overcome – for example – the large amount of missing data that we encountered when analysing the case reports for **Chapter 8**. A validated quality check should include essential components such as a clear and thorough presentation of clinical data, an in-depth exploration of differential diagnoses (if applicable), and a well-reasoned discussion of the impact of the intervention. In addition, it should assess the clinical relevance of the case and whether the findings provide actionable insights for clinical practice or future research.

To ensure the validity of such a quality check, a robust development process is required. The development of a core dataset for case reports or small case series should be unanimous and based on a multidisciplinary view. A Delphi consensus process involving experts in clinical research, case reporting, and evidence-based medicine, would be necessary to define the core criteria. [19] The checklist should then be tested for inter-rater reliability by having multiple reviewers assess the same case reports independently, using statistical measures

like Cohen's kappa to evaluate consistency. Finally, the tool's applicability across various specialties and settings should be confirmed to ensure its broad utility. By establishing validated quality checks, the reliability of case reports can be enhanced, allowing them to contribute more effectively to the available evidence, particularly in fields where large-scale studies are not feasible, as we have seen in cancer during pregnancy. Case-reports meeting these criteria should be a higher level of evidence in the EBM pyramid, as suggested in Figure 5.

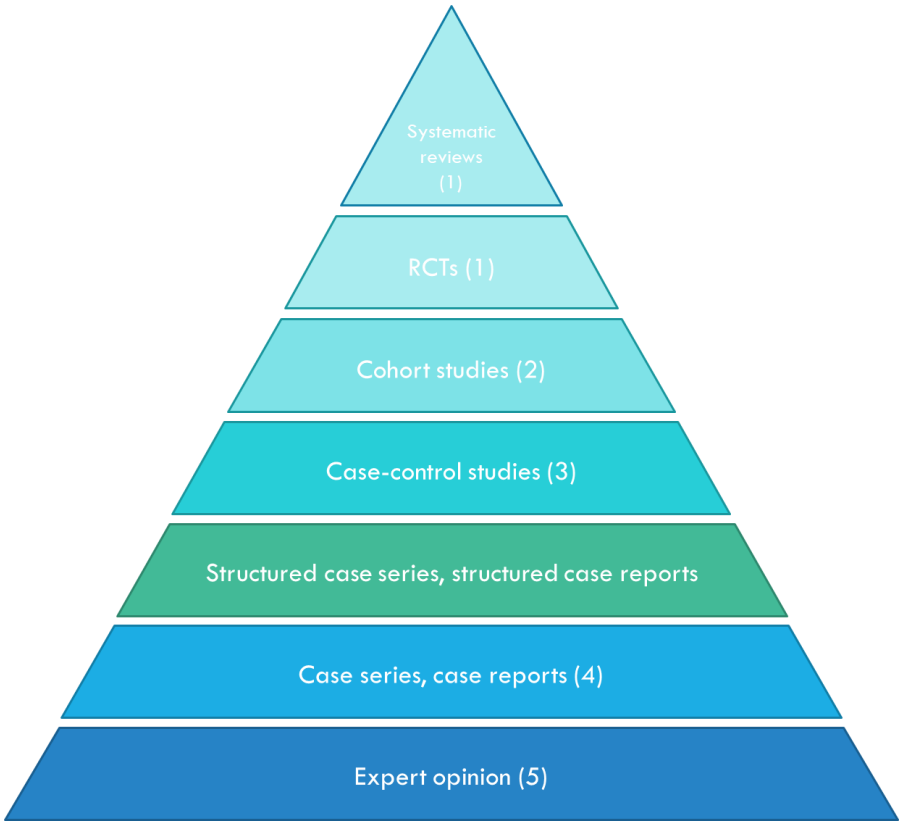


Figure 5. Suggestion of new EVM levels of evidence pyramid. According to the EBM levels of evidence pyramid, the quality of evidence increases and the risk of bias decreases with increasing levels of the pyramid.

Novel treatment options during pregnancy

One of the key gaps in knowledge mentioned in this thesis, is the use of novel treatment options during pregnancy. In the younger cancer population, proton therapy, targeted therapies and immunotherapy are increasingly being used. These treatment modalities are becoming crucial, especially for patients with good performance status, which is often seen in younger patients of reproductive age. As cancer treatments evolve, these therapies have the potential to significantly improve survival and preserve organs.

Before this thesis, only a limited number of case reports concerning the administration of immunotherapy during pregnancy were available in the literature[20-26] with generally reassuring but short-term outcomes. In this thesis, specific aspects of novel cancer treatments during pregnancy, with a focus on immunotherapy and proton therapy, were addressed in **Chapters 10, 11 and 12**. Since the publication of these papers, further research has been conducted. [27-30] A retrospective study by Dupere et al. [27] evaluating pencil beam scanning proton therapy for seven pregnant women with brain and head and neck cancers, confirmed the preference

of using proton therapy over the conventional photon-based treatments, as was also concluded by us in **Chapter 12**. Piemonti et al. [30] published a case of probable immune-related necrotizing enterocolitis after in utero exposure to pembrolizumab, underscoring the warning in our case report in **Chapter 11.** Finally, related to our paper regarding the use of immunotherapy during pregnancy, Gougis et al. [29] published a paper describing a cohort of 3558 cases registered in the WHO international pharmacovigilance database VigiBase including women with anticancer agent exposure during pregnancy. They describe 91 women exposed to immune checkpoint inhibitors (ICIs) during pregnancy and found no increase of adverse events. However, no information on duration, follow up, nor timing of administration during pregnancy was available within this cohort.

Based on the scarce literature and the information provided by this thesis, the measured models and short-term results of proton therapy seem reassuring. Based on a handful of case series and a theoretical review of literature, ICIs in pregnancy should be used with caution, mainly because of irAEs. This is not valid in all patients, and in some cases cancer treatment with ICIs is unavoidable during pregnancy as they are the preferred treatment modality. Pharmacokinetic studies and cohort analyses with adequate follow-up are needed to provide more substantiated answers to the difficulties faced by pregnant women in need of systemic cancer treatment, and to formulate guidelines regarding the possibilities or impossibilities of these novel therapies.

Elaborate on cancer (treatment) during breastfeeding

Over the last couple of years, the ABCIP received an increasing amount of questions regarding the ability to continue or start breastfeeding while administering systemic cancer treatment. Although current research has primarily focused on a balance between fetal safety of cancer treatment and maternal survival, future research should also focus on the possibilities of breastfeeding during or after treatment, to not overlook the long-term benefits of breastfeeding for both mother and child. Published literature raises important concerns about the transfer of drugs into breast milk, but the available evidence remains scarce.[31-36] Future research is crucial to establish clear guidelines for women who wish to breastfeed after treatment in the postpartum period. Initial studies exploring the pharmacokinetics of various agents in breast milk have shown relatively low relative infant doses (RIDs) for drugs like cyclophosphamide and carboplatin, particularly when the milk is discarded for 1-3 days after administration.[36] However, doxorubicin was measured at high concentrations in breast milk after administering R-CHOP.[31] For nivolumab, the cumulative RID over the first cycle was high, with even higher concentrations following the second cycle.[37] These early findings show that there are possibilities for women who are eager to breastfeed while treated with some drugs, but it is essential to investigate the pharmacokinetics of each agent thoroughly. Expanding our understanding of the pharmacokinetics of these treatments in lactating women and their potential impact on infants, will provide better recommendations to clinicians treating women who wish to breastfeed during cancer treatment, ensuring both safety and optimal care for the relationship between mother and child.

Psychological support for mother and family

ABCIP seeks to provide information to requesting physicians on how to support pregnant women with cancer and their families, not only in terms of treatment, but also by recommending appropriate psychological support. In addition to the previously mentioned rare cancer types and novel treatment modalities, psychological support remains an area of importance to the management of pregnant women with cancer that is currently under-researched. It is becoming increasingly important as treatment options and prognoses evolve. As Vandenbroucke et al. demonstrated back in 2017, women with a cancer diagnosis during pregnancy and their partners had elevated levels of distress.[38] Consequently, they recommend counselling with a qualified psychologist during or after treatment. Next to this, a systematic review by Kagawa et al. indicate that fertility issues and lack of information about reproductive health for pregnant women with cancer and cancer survivors lead to physical, psychological and social challenges.[39] Investigating the most appropriate psychological support for patients and their families may be a focus for future research.

Palliative care during pregnancy

Lastly, as most literature in the field of cancer in pregnancy is optimistic and likes to prefer to show the possibilities where possible, we have to realize that not all malignancies are curable, particularly in cases of metastatic disease, as is exemplified in **Chapter 7**, describing all cases of maternal death during pregnancy in the INCIP. Within the ABCIP, requests for adequate palliative treatment options during pregnancy and care for the families have been asked. Therefore, it is of utmost importance to understand the needs of those families facing a future without their mother, potentially even without a viable pregnancy due to maternal death. Providing information about palliative care during pregnancy and exploring the needs of the partner and children (where appropriate) will increase knowledge for clinicians faced with these difficult situations. Future research focusing on bereaved families who have had to cope with the death of a mother due to cancer in pregnancy, with follow-up using validated questionnaires about care and support needs, may inform us about the most appropriate care plan and recommendations.

CONCLUSION

This thesis demonstrates that the establishment of the ABCIP is highly appreciated and is consulted on a daily basis to combine the latest evidence with consensus where necessary for patient-specific situations. The research conducted in this thesis provides an overview of the working methods of the ABCIP and shows the impact of the ABCIP on physicians using it. Next to this, the ABCIP identifies and investigates the gaps in knowledge based on real-world questions received by the board.

The ABCIP underscores the importance of an international, multidisciplinary approach to provide the most accurate care to pregnant women with cancer. By uniting efforts with the INCIP registry and latest research initiatives, the potential for gathering critical follow-up data increases, especially for rare and complex cases where local expertise may be limited. Where high-level evidence is lacking, the ABCIP facilitates the exchange

of expertise across borders, fostering a global network of healthcare professionals who can contribute to and benefit from the INCIP's findings. In addition, the ABCIP provides the INCIP with novel topics to investigate.

The ongoing effort to expand knowledge on cancer during pregnancy, relies heavily on the professionalization and internationalization of initiatives like the INCIP database. As this thesis highlights, the INCIP has evolved into an invaluable resource, providing critical data on the management of cancer in pregnancy across various tumor types and treatment modalities. However, to further close the gaps in evidence-based knowledge, particularly for rare cancers, the database must continue to grow and adapt. Expanding the INCIP's reach to include more countries would significantly enhance the collection of data on uncommon cancer types, providing the robust, real-world evidence needed to refine treatment protocols and inform clinical guidelines.

The crux can be found in the words of Gabbay and Le May when discussing their concept of mindlines:

'Moving from the linear rationalism of guidelines to the complex wisdom of good practice'

This may prove to be a key tool in optimizing care for pregnant women with cancer. A crucial element of this is a guiding principle that also encapsulates what we sought to achieve with the ABCIP, and hopefully what will be remembered about our working methods: fostering respectful critical dialogue and collaborative sense-making.

REFERENCES

1. Stensheim H, Møller B, Van Dijk T, D. FS. Cause-specific survival for women diagnosed with cancer during pregnancy or lactation: A registry-based cohort study. *Journal of Clinical Oncology* **27**(1): 45-51 (2009).
2. de Haan J, Verheecke M, Van Calsteren K, et al. Oncological management and obstetric and neonatal outcomes for women diagnosed with cancer during pregnancy: a 20-year international cohort study of 1170 patients. *The Lancet Oncology* **19**(3): 337-46 (2018)
3. van Gerwen M, Maggen C, Cardonick E, et al. Association of Chemotherapy Timing in Pregnancy With Congenital Malformation. *JAMA Netw Open* **4**(6): e2113180 (2021).
4. Amant F, Nekljudova V, Maggen C, et al. Outcome of breast cancer patients treated with chemotherapy during pregnancy compared with non-pregnant controls. *Eur J Cancer* **170**: 54-63 (2022).
5. Greenberg LH, Verdes P, Tanaka KR. Congenital Anomalies Probably Induced by Cyclophosphamide. *Jama* **188**(5): 423-6 (1964).
6. Durie BG, Giles HR. Successful treatment of acute leukemia during pregnancy. Combination therapy in the third trimester. *Arch Intern Med* **137**(1): 90-1 (1977).
7. Ortega J. Multiple agent chemotherapy including bleomycin of non-Hodgkin's lymphoma during pregnancy. *Cancer* **40**(6): 2829-35 (1977).
8. Durodola JI. Administration of cyclophosphamide during late pregnancy and early lactation: a case report. *J Natl Med Assoc* **71**(2): 165-6 (1979)
9. Pizzuto J, Aviles A, Noriega L, Niz J, Morales M, Romero F. Treatment of acute leukemia during pregnancy: presentation of nine cases. *Cancer Treat Rep* **64**(4-5): 679-83 (1980).
10. Zemlickis D, Lishner M, Degendorfer P, Panzarella T, Sutcliffe SB, Koren G. Fetal outcome after in utero exposure to cancer chemotherapy. *Arch Intern Med* **152**(3): 573-6 (1992).
11. Gwyn K. Children Exposed to Chemotherapy In Utero. *JNCI Monographs* **2005**(34): 69-71 (2005).
12. Gabbay J, May Al. Evidence based guidelines or collectively constructed "mindlines?" Ethnographic study of knowledge management in primary care. *BMJ* **329**(7473): 1013 (2004)
13. Lander B, Balka E. Exploring How Evidence is Used in Care Through an Organizational Ethnography of Two Teaching Hospitals. *J Med Internet Res* **21**(3): e10769 (2019).
14. Commission E. Conference Report. 3rd Conference on European Reference Networks; 2017 March 9-10. 2017 (accessed Jan 27th 2021).

15. Directive 2011/24/EU of the European Parliament and of the Council of 9 March 2011 on the Application of Patients' Rights in Cross-Border Healthcare. Available online at: http://data.europa.eu/eli/dir/2011/24/oj; (accessed: Oct 10th 2024)
16. Clinical Patient Management System (CPMS). https://cpms.ern-net.eu/login/ (accessed Oct 10th 2024.
17. White EK, Wagner IV, van Beuzekom C, et al. A critical evaluation of the EU-virtual consultation platform (CPMS) within the European Reference Network on Rare Endocrine Conditions. *Endocr Connect* **11**(11) (2022).
18. Moola S MZ, Tufanaru C, Aromataris E, Sears K, Sfetcu R, Currie M, Qureshi R, Mattis P, Lisy K, Mu P-F. . Chapter 7: Systematic reviews of etiology and risk. In: Aromataris E MZe, ed. JBI Manual for Evidence Synthesis: JBI; 2020. Available from https://synthesismanual.jbi.global. (accessed Sept 23th 2024)
19. Nasa P, Jain R, Juneja D. Delphi methodology in healthcare research: How to decide its appropriateness. *World J Methodol* **11**(4): 116-29 (2021).
20. Menzer C, Beedgen B, Rom J, et al. Immunotherapy with ipilimumab plus nivolumab in a stage IV melanoma patient during pregnancy. *Eur J Cancer* **104**: 239-42 (2018)
21. Mehta A, Kim KB, Minor DR. Case Report of a Pregnancy During Ipilimumab Therapy. *Journal of global oncology* **4**: 1-3 (2018).
22. Burotto M, Gormaz JG, Samtani S, et al. Viable Pregnancy in a patient with metastatic melanoma treated with double checkpoint immunotherapy. *Seminars in oncology* **45**(3): 164-9 (2018).
23. Xu W, Moor RJ, Walpole ET, Atkinson VG. Pregnancy with successful foetal and maternal outcome in a melanoma patient treated with nivolumab in the first trimester: case report and review of the literature. *Melanoma Res* **29**(3): 333-7 (2019).
24. Bucheit AD, Hardy JT, Szender JB, Glitza Oliva IC. Conception and viable twin pregnancy in a patient with metastatic melanoma while treated with CTLA-4 and PD-1 checkpoint inhibition. *Melanoma Res* **30**(4): 423-5 (2020).
25. Haiduk J, Ziemer M. Pregnancy in a patient with metastatic uveal melanoma treated with nivolumab. *J Dtsch Dermatol Ges* (2021).
26. Polnaszek B, Mullen M, Bligard K, Raghuraman N, Massad LS. Term Pregnancy After Complete Response of Placental Site Trophoblastic Tumor to Immunotherapy. *Obstetrics & Gynecology* **138**(1): 115-8 (2021).
27. Dupere JM, Lucido JJ, Breen WG, et al. Pencil Beam Scanning Proton Therapy for Pregnant Patients With Brain and Head and Neck Cancers. *International journal of radiation oncology, biology, physics* **118**(3): 853-8 (2024)
28. Rahimi R, Taylor M, Li X, et al. Fetal dose assessment in a pregnant patient with brain tumor: A comparative study of proton PBS and 3DCRT/VMAT radiation therapy techniques. *J Appl Clin Med Phys* **25**(8): e14394 (2024).
29. Gougis P, Hamy A-S, Jochum F, et al. Immune Checkpoint Inhibitor Use During Pregnancy and Outcomes in Pregnant Individuals and Newborns. *JAMA Network Open* **7**(4): e245625-e (2024).
30. Piemonti L, Vettor L, Contro E. A Case Report of Metastatic Gastric Cancer Treated with Pembrolizumab during Pregnancy. *Fetal Diagn Ther* **51**(5): 493-9 (2024).
31. Codacci-Pisanelli G, Honeywell RJ, Asselin N, et al. Breastfeeding during R-CHOP chemotherapy: please abstain! *Eur J Cancer* **119**: 107-11 (2019).
32. Jackson C, Morris T, Hung N, Hung T. Breast milk paclitaxel excretion following intravenous chemotherapy-a case report. *Br J Cancer* **121**(5): 421-4 (2019).
33. Griffin SJ, Milla M, Baker TE, Liu T, Wang H, Hale TW. Transfer of carboplatin and paclitaxel into breast milk. *J Hum Lact* **28**(4): 457-9 (2012).
34. Hays KE, Ryu RJ, Swisher EM, et al. Duration of cisplatin excretion in breast milk. *J Hum Lact* **29**(4): 469-72 (2013).
35. Damoiseaux D, Amant F, Beijnen JH, et al. Physiologically-based pharmacokinetic model to predict doxorubicin and paclitaxel exposure in infants through breast milk. *CPT Pharmacometrics Syst Pharmacol* **12**(12): 1931-44 (2023).
36. Damoiseaux D, Calpe S, Rosing H, et al. Presence of Five Chemotherapeutic Drugs in Breast Milk as a Guide for the Safe Use of Chemotherapy During Breastfeeding: Results From a Case Series. *Clin Pharmacol Ther* **112**(2): 404-10 (2022).
37. de Jong K, Damoiseaux D, Pluim D, et al. High accumulation of nivolumab in human breast milk: A case report. *Biomed Pharmacother* **166**: 115354 (2023).
38. Vandenbroucke T, Han SN, Van Calsteren K, et al. Psychological distress and cognitive coping in pregnant women diagnosed with cancer and their partners. *Psycho-Oncology* (2017).
39. Kagawa K, Yoshikawa Y, Koizumi T, Suzuki N. Psychological Aspects of and Support for Survivors Attempting to Conceive During or After Cancer Treatments: A Mixed-Methods Systematic Review. *Journal of Adolescent and Young Adult Oncology* (2024).

Appendices

Scientific summary

PART I INTROUDCTION

Chapter 1 provides a general introduction to this thesis investigating the impact of an international advisory board on the management of cancer in pregnancy. Because cancer in pregnancy is so rare, most clinicians who see these patients lack the expertise and confidence to diagnose and treat them. There is also a lack of high-level scientific evidence (using the evidence-based medicine pyramid) on treatment options and pregnancy outcomes. Knowledge of most new treatments and rare situations is mainly based on case reports or case series. **Chapter 2** reviews the state of the art regarding the management of pregnancy in women with cancer at the beginning of this PhD trajectory, discussing the different treatment modalities that can be used during pregnancy and the need for a multidisciplinary team including specialists with relevant expertise. In **Chapter 3** the objectives of this thesis are outlined. We tried to evaluate the impact of a multidisciplinary advisory board (MDAB) in the context of cancer in pregnancy. Secondly, we wanted to tackle knowledge gaps encountered by the MDAB using data from the INCIP and the cases identified by an MDAB.

PART II POOLING KNOWLEDGE: AN ADVISORY BOARD ON CANCER, INFERTILTY AND PREGNANCY

Part II highlights efforts to pool knowledge and standardize care through multidisciplinary collaboration. In order to provide the best possible care for pregnant women with cancer, the Advisory Board on Cancer in Pregnancy (ABCIP) was established during the course of this PhD. **Chapter 4** presents the results of an international survey on the organisation of care for pregnant women with cancer. Responses from 249 physicians working in 36 countries revealed a wide variation in the organisation of care, a lack of centralisation, and a lack of knowledge about the management of pregnant women with cancer. There was a need for more structured consultation processes, such as centralisation or the establishment of advisory boards. **Chapter 5** describes ten years of experience with the *'Adviesgroep Kanker tijdens de Zwangerschap'*, a national MDAB in the Netherlands. During this period, 213 recommendations were made regarding the preferred and safest options for imaging, treatment options during pregnancy, possible effects on the child, and fertility-preserving options. A questionnaire sent to all physicians who consulted the Dutch MDAB was completed by 50 physicians. It showed a high level of satisfaction with the recommendations. The physicians felt supported by the recommendations they received.
Based on the information from the previous chapters, **Chapter 6** discusses the development of the ABCIP, an on-demand virtual tumour board that allows international consultation in real time. All experts can discuss incoming submissions at any time in a secure forum. All input is later compiled into a formal personalised recommendation, which is returned to the requesting physician within 7 days. In addition to the international ABCIP, there are also Belgian, Danish, Dutch, Polish and Spanish-IberoAmerican groups online.

PART III CLINICAL CHALLENGES IN THE FIELD OF CANCER IN PREGNANCY

Based on specific cases encountered in the ABCIP, where scientific evidence is sometimes lacking, Part III addresses clinical challenges associated with cancer in pregnancy. **Chapter 7** provides a descriptive analysis of 131 cases of maternal death from cancer during pregnancy, based on data from INCIP. It compares all cases of women with cancer who died during pregnancy, childbirth or within 1 year postpartum with all women with cancer who survived the first year postpartum. Maternal mortality occurred in 5.6% of all cases of cancer in pregnancy and is associated with fewer live births (75.6%; 99/131 vs 90.0%; 1952/2163, $p<0.001$), more elective caesarean sections (60.4%; 64/104 vs 41.2%; 756/1836), $p<0.001$) and a lower gestational age at (induced) delivery (34.0 vs 37.1 weeks, $p<0.001$), resulting in more preterm births. The chapter concludes that awareness of the possibility of maternal death from cancer and early identification of women at risk of poor maternal outcome allows for a fair discussion with the woman and her partner and the initiation of appropriate palliative care, including psychological support for the family after the maternal death. **Chapter 8** reports on the obstetrical and oncological outcomes of 162 patients diagnosed with sarcoma during pregnancy, combining 45 case data from the INCIP with 117 cases retrieved with a review of the literature. It showed that metastatic disease was present in 25.6% of patients. Common symptoms at presentation included a growing mass, pain and dyspnoea. Surgery (38.9%) and chemotherapy (17.3%) were the most common treatments during pregnancy. Fifty-five patients underwent induction of labour and 14 first trimester abortions. Known obstetric outcomes of 147 patients were 83% live births, 9.5% abortions and 3.4% stillbirths. 56.3% underwent elective caesarean section. 65.2% of live births were preterm. The median birth weight was 2375 grams (690-4465) and 3.8% of the new born had congenital malformations. Of 136 patients with known oncological follow-up, the median follow-up was 22 months (0-160), the recurrence rate was 43.4%, and the maternal mortality rate was 38.2%. The chapter highlights the often poor prognosis of sarcoma during pregnancy. Pregnancy-mimicking symptoms may explain the high percentage of metastatic disease at diagnosis. It shows that cancer treatment is possible during pregnancy and that preterm delivery should be avoided whenever possible. The heterogeneity of the different tumour subtypes and the variety of symptoms make it difficult for doctors to formulate a single set of recommendations for this group of patients.

To improve knowledge of the diagnosis and management of haematological malignancies in pregnancy, **Chapter 9** provides a summary of the use of diagnostic modalities and treatment options, including chemotherapy, radiotherapy, targeted therapy and immunotherapy for acute leukaemia, Hodgkin's lymphoma, non-Hodgkin's lymphoma, myeloproliferative disorders, aplastic anaemia and multiple myeloma in pregnancy. And to broaden the information available on the use of immunotherapy during pregnancy, **Chapter 10** summarises preclinical and clinical data related to the use of immunotherapy during pregnancy, including all approved immune checkpoint inhibitors, recombinant cytokines, cell therapies, vaccines and immunomodulatory drugs.

During the course of this PhD, we came across some situations that had not previously been described in the literature, but were of great importance to the cancer in pregnancy community and the work of ABCIP. **Chapter 11** discusses a case of severe immune-related enteritis in a child caused by in utero exposure to pembrolizumab. This case illustrates the potential of immune checkpoint inhibitors to cause immune-related adverse events in offspring, even several months after birth, and reinforces the recommendation that these drugs should be used with great caution during pregnancy. **Chapter 12** describes the first detailed report of proton therapy as a cancer treatment in a pregnant patient with nasopharyngeal carcinoma. Phantom measurements showed a thirty-fold reduction in fetal radiation dose with proton therapy compared with photon therapy. Following proton therapy during pregnancy, a healthy boy was born at 39 weeks' gestation with a birth weight in the 83rd percentile. Paediatric follow-up at 2 months of age showed normal growth and age-appropriate motor development with no evidence of neurological problems. Follow-up of the tumour 3 months after completion of treatment showed complete remission. This case demonstrates the potential of proton therapy for treatment during pregnancy.

PART IV GENERAL DISCUSSION AND CONCLUSION

Part IV provides a comprehensive discussion of the findings of this thesis. We mention the importance of case reports in terms of their signalling function. We also give some warnings about the use of case report findings in clinical care. We suggest the use of mindlines when evidence-based medicine is difficult to implement due to the lack of high-level evidence. Part IV also describes the establishment of the ABCIP during the course of this doctoral programme, its advantages, limitations and future prospects.
In addition, we discuss the expansion of future knowledge on cancer in pregnancy by proposing the use of validated quality checks for case reports. We suggest that knowledge of new treatment modalities during pregnancy and the use of systemic cancer treatment during breastfeeding should be increased through the use of pharmacokinetic studies and cohort analyses. Important areas of concern for pregnant women with cancer, their families and clinicians could be investigating the need for psychological support for the mother and family and increasing knowledge of palliative care during pregnancy.

Samenvatting

DEEL I INTRODUCTIE

Dit proefschrift onderzoekt hoe kanker tijdens de zwangerschap beter kan worden behandeld, met een focus op hoe internationale adviesgroepen de zorg kunnen verbeteren. Omdat kanker tijdens de zwangerschap zeldzaam is, ontbreekt het de meeste artsen die deze patiënten zien aan de expertise en het vertrouwen om ze te diagnosticeren en te behandelen. Daarnaast is er weinig wetenschappelijk bewijs van hoog niveau over de behandelmogelijkheden en de uitkomsten voor moeder en kind. Kennis over nieuwe behandelingen en zeldzame situaties is voornamelijk gebaseerd op een handvol casussen. In **Hoofdstuk 2** hebben we de behandelmogelijkheden voor zwangeren met kanker beschreven zoals bekend was aan het begin van dit promotietraject in 2020. We probeerden de impact van een multidisciplinaire adviesgroep in de context van kanker in de zwangerschap te onderzoeken. Daarnaast wilden we kennishiaten aanpakken waarmee zo'n adviesgroep werd geconfronteerd, door gebruik te maken van gegevens van de internationale database voor kanker tijdens de zwangerschap (de INCIP) en de casussen die door de adviesgroep werden geïdentificeerd.

DEEL II KENNIS BUNDELEN: EEN ADVIESGROEP VOOR KANKER, INFERTILITEIT EN ZWANGERSCHAP

Om de best mogelijke zorg te kunnen bieden aan zwangere vrouwen met kanker, beschrijft dit proefschrift de oprichting van de Advisory Board on Cancer in Pregnancy (ABCIP). **Hoofdstuk 4** laat de resultaten van een internationaal vragenlijst onderzoek naar de organisatie van de zorg voor zwangere vrouwen met kanker zien, waaruit een grote variatie in organisatie van zorg, een gebrek aan centralisatie en een gebrek aan kennis over de behandeling van zwangere vrouwen met kanker blijkt.. In **Hoofdstuk 5** beschrijven we tien jaar ervaring met de *'Adviesgroep Kanker tijdens het Zwangerschap'*, een landelijke adviesgroep in Nederland.

Op basis van alle opgedane kennis hebben we de ABCIP ontwikkeld. **Hoofdstuk 6** beschrijft de werking van de ABCIP. Artsen uit de hele wereld kunnen complexe casussen indienen bij dit virtuele platform en binnen een week advies krijgen van experts. Dit helpt om de zorg te standaardiseren en ervoor te zorgen dat zelfs zeldzame of ingewikkelde gevallen profiteren van de kennis van meerdere specialisten.

DEEL III KLINISCHE UITDAGINGEN OP HET GEBIED VAN KANKER IN DE ZWANGERSCHAP

Deel III van het proefschrift richt zich op de medische uitdagingen bij de behandeling van kanker tijdens de zwangerschap. **Hoofdstuk 7** onderzocht een groep vrouwen met kanker die tijdens de zwangerschap, tijdens de bevalling of binnen 1 jaar na de bevalling overleden. We zagen in vergelijking met vrouwen die niet overleden minder levengeborenen, meer keizersnedes en meer vroeggeboortes. Het hoofdstuk concludeert dat bewustwording van de mogelijkheid van maternale sterfte door kanker en vroegtijdige opsproing van vrouwen met een verhoogd risico op vroegtijdig overlijden, een eerlijk gesprek met de vrouw en haar partner mogelijk maakt. In **Hoofdstuk 8** beschreven we een groep vrouwen bij wie tijdens de

zwangerschap een sarcoom werd vastgesteld, uit de INCIP en de literatuur. Het hoofdstuk benadrukt de vaak slechte prognose van sarcomen tijdens de zwangerschap. Zwangerschapsverschijnselen kunnen het hoge percentage gemetastaseerde ziekte bij diagnose verklaren. Het laat zien dat de behandeling van kanker mogelijk is tijdens de zwangerschap en dat vroeggeboorte waar mogelijk moet worden vermeden.

Om de kennis over de diagnose en behandeling van hematologische kankers (zoals bijvoorbeeld leukemie, multipel myeloom of lymfoom) tijdens de zwangerschap te verbeteren, geeft **Hoofdstuk 9** een overzicht van het gebruik van onderzoeken en behandelingen, waaronder chemotherapie, bestraling, doelgerichte therapie en immuuntherapie voor alle soorten hematologische kankers tijdens de zwangerschap. En om de beschikbare informatie over het gebruik van immuuntherapie tijdens de zwangerschap te verbreden, geeft **hoofdstuk 10** een samenvatting van informatie met betrekking tot het gebruik van alle bekende vormen van immuuntherapie tijdens de zwangerschap.

We hebben ook twee casussen beschreven in dit proefschrift, van groot belang voor de gemeenschap die te maken krijgt met kanker in de zwangerschap en het werk van ABCIP. **Hoofdstuk 11** bespreekt een ernstige bijwerking bij een pasgeboren kind veroorzaakt door blootstelling aan pembrolizumab tijdens de zwangerschap (een vorm van immuuntherapie). Het laat een mogelijk risico zien van deze nieuwe middelen, zelfs enkele maanden na de geboorte, en versterkt de aanbeveling dat deze geneesmiddelen met grote voorzichtigheid moeten worden gebruikt tijdens de zwangerschap. **Hoofdstuk 12** beschrijft het eerste gedetailleerde verslag van protontherapie (een nieuwe vorm van bestraling) als kankerbehandeling bij een zwangere patiënt met kanker van de neusholte. Metingen gedaan op een fantoom toonden een dertigvoudige vermindering van de straling voor het ongeboren kind bij protontherapie in vergelijking met de nu veel gebruikte vorm van straling: photontherapie. De casus beschrijft positieve uitkomsten van moeder en kind en toont hiermee het potentieel aan van protontherapie voor behandeling tijdens de zwangerschap.

DEEL IV ALGEMENE DISCUSSIE EN CONCLUSIE

De bevindingen van dit proefschrift benadrukken het belang van internationale samenwerking en doorlopend onderzoek om de bestaande kennishiaten te vullen. Door data te bundelen en expertise te delen, kan de kwaliteit van zorg en de uitkomsten voor zwangere vrouwen met kanker aanzienlijk verbeteren. We benadrukken het belang van casusbeschrijvingen met betrekking tot hun signaalfunctie, en doen in **Deel IV** voorstellen voor vervolgonderzoek. We suggereren dat de kennis over nieuwe behandelingsmodaliteiten tijdens de zwangerschap en het gebruik van systemische kankerbehandeling tijdens de borstvoeding moet worden vergroot door het gebruik van studies in het lab naar de mogelijke effecten van deze vormen van therapie in het lichaam van moeder, kind of in moedermelk. Belangrijke aandachtspunten voor zwangere vrouwen met kanker, hun families en dokters zouden kunnen zijn het

onderzoeken van de behoefte aan psychologische ondersteuning voor de moeder en de familie en het vergroten van de kennis over palliatieve zorg tijdens de zwangerschap. Dit proefschrift vormt een belangrijke stap vooruit om ervoor te zorgen dat zelfs in de meest complexe situaties patiënten veilige, op bewijs gebaseerde en persoonlijke zorg ontvangen door middel van een multidisciplinaire adviesgroep als de ABCIP.

List of abbreviations

18FDG-PET/CT	Fluorine-18-flurodeoxyglucose positron emission tomography integrated with computed tomography
ABCIP	Advisory Board on Cancer, Infertility and Pregnancy
ADCs	Antibody-drug conjugates
AKZ	Adviesgroep Kanker en Zwangerschap
ALL	Acute lymphocytic leukemia
AML	Acute myeloid leukemia
APECED	Autoimmune phenomena, polyendocrinopathy, candidiasis, and ectodermal dystrophy
BiTEs	Bispecific T-cell engagers
CAR(T)	Chimeric antigen receptor (T-cell)
CBCT	Cone beam CT
cfDNA	Cell-free DNA
CIP-MDT	Multidisciplinary tumour board for cancer, infertility and pregnancy
CLL	Chronic lymphocytic leukemia
CML	Chronic myeloid leukemia
CPMS	Clinical Patient Management System
CT	Computed tomography
CTCAE 4.0	Common Terminology Criteria for Adverse Events version 4.0
CTV	Clinical target volume
DLBCL	Diffuse large B-cell lymphoma
EBM	Evidence based medicine
EBV	Epstein-Barr virus
ERNs	European Reference Networks
ESGO	European Society of Gynaecological Oncology
ESMO	European Society or Medical Oncology
ET	Essential thrombocytopenia
FGR	Fetal growth restriction
FOXP3	Forkhead box P3
FVM	Fetal vascular malperfusion
HL	Hodgkin lymphoma
HSV-1	Herpes simplex virus type 1
ICD-10	International Classification of Diseases, tenth revision
ICIs	Immune checkpoint inhibitors
IFNγ	Interferon γ
IL-2	Interleukin 2
IMPT	Intensity modulated proton therapy
INCIP	International Network of Cancer, Infertility and Pregnancy
IPEX	Immune dysregulation, polyendocrinopathy, enteropathy, X-linked syndrome
irAE	Immune-related adverse events
JBI	Joanna Briggs Institute
LMWH	Low molecular weight heparins
MDAB	Multidisciplinary advisory board
MDT	Multidisciplinary oncological team / tumour board
MMBRACE-UK	Mothers and Babies: Reducing Risk through Audits and Confidential Enquiries across the United Kingdom
MPN	Myeloproliferative neoplasma
MTX	Methotrexate
MVM	Maternal vascular malperfusion
NHL	Non-Hodgkin lymphoma
NIPT	Non-invasive prenatal testing
NSTS	Non-soft tissue sarcoma

NTRK	Neurotrophic tyrosine receptor kinase
PBS	Pencil Beam Scanning
PD-1	Programmed cell death protein 1
PD-L1	Programmed cell death protein ligand 1
PET	Positron Emission Tomography
PV	Polycythemia vera
RCT	Randomized controlled trials
RID	Relative infant dose
SEER	Surveillance, Epidemiology, and End Results (A program for cancer statistics in the USA)
SGA	Small for gestational age
STS	Soft tissue sarcoma
Th	T helper
TKIs	Tyrosine kinase inhibitor
TNFα	Tumour necrosis factor α
TOP	Termination of pregnancy
TPO-RA	Thrombopoietin receptor agonists
WB-DWI/MRI	Whole body magnetic resonance imaging with diffusion-weighted sequence
WHO	World Health Organization

Supplementary appendix

Chapter 4

The supplementary appendix can be found here: downloadSupplement (wiley.com)

Chapter 5

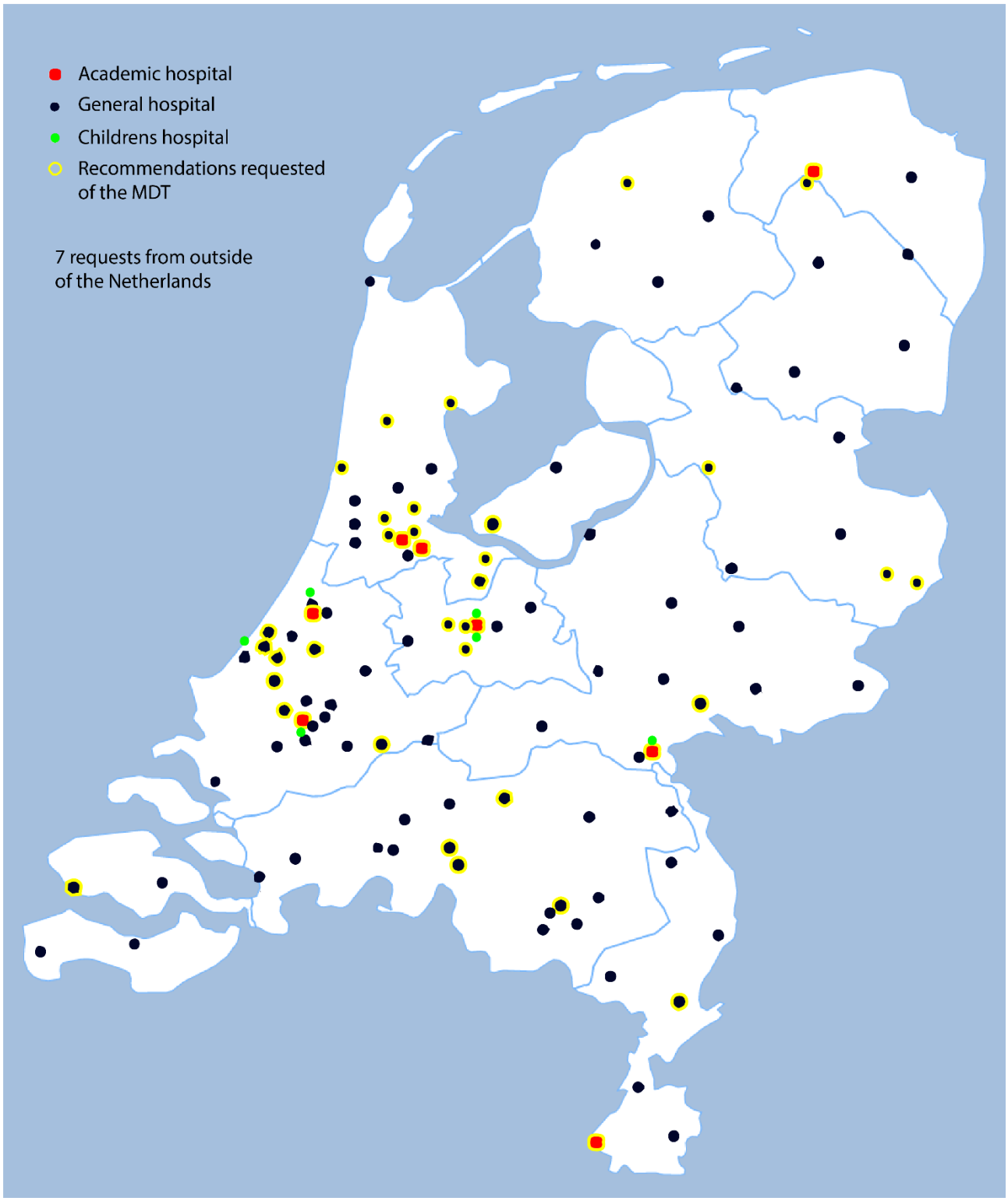
Appendix 1

Questionnaire sent out to 93 physicians from the Netherlands that requested advice from the CIP-MDT from 2012 to October 2020.

1. In what type of medical center were you working at the time of the request for advice?
2. How many times have you sought advice from the Dutch CIP-MDT?
3. On which topics did you seek advice? (Multiple answers possible)
4. How did you hear about the existence of the Dutch CIP-MDT?
5. How did you contact the Dutch CIP-MDT?
6. Was the Dutch CIP-MDT easy to reach?
7. Would you contact the Dutch CIP-MDT again for advice?
8. Would you recommend the Dutch CIP-MDT to your colleagues?
9. Did you tell your patient that you had consulted the Dutch CIP-MDT?
10. Did you also tell your patient about the INCIP (International Network on Cancer, Infertility and Pregnancy) study on Cancer and Pregnancy?
11. Had you formulated your own treatment plan before consulting the Dutch CIP-MDT?
12. To what extent were you satisfied with the advice given?
13. Did the advice differ from your own proposed treatment plan?
14. Was the advice sufficiently clear?
15. To what extent was the advice innovative?
16. To what extent was the advice innovative?
17. Why did you follow/partly follow/not follow the advice?
18. Did you feel supported in your treatment plan by the advice given?
19. Did you add the advice letter to your patient's medical file?
20. Was it pleasant to receive references to the advice?
21. Did you receive the advice from the Dutch CIP-MDT in time?
22. Were you satisfied with the speed of the advice given?
23. The Dutch CIP-MDT nowadays adds extra general information on cancer and pregnancy, is this desirable?
24. If you have asked the Dutch CIP-MDT for advice on more than one occasion and would like additional information on the other advices, you can fill this out below:
25. What is your opinion about asking for advice via a website?
26. Do you have any tips or remarks for the advisory group?
27. May we contact you if you have questions or do you want to be kept informed of developments regarding the Dutch CIP-MDT and the international platform? Then please fill in your e-mail address below
28. We would like to use the answers given for scientific research. Do you give your consent for this?

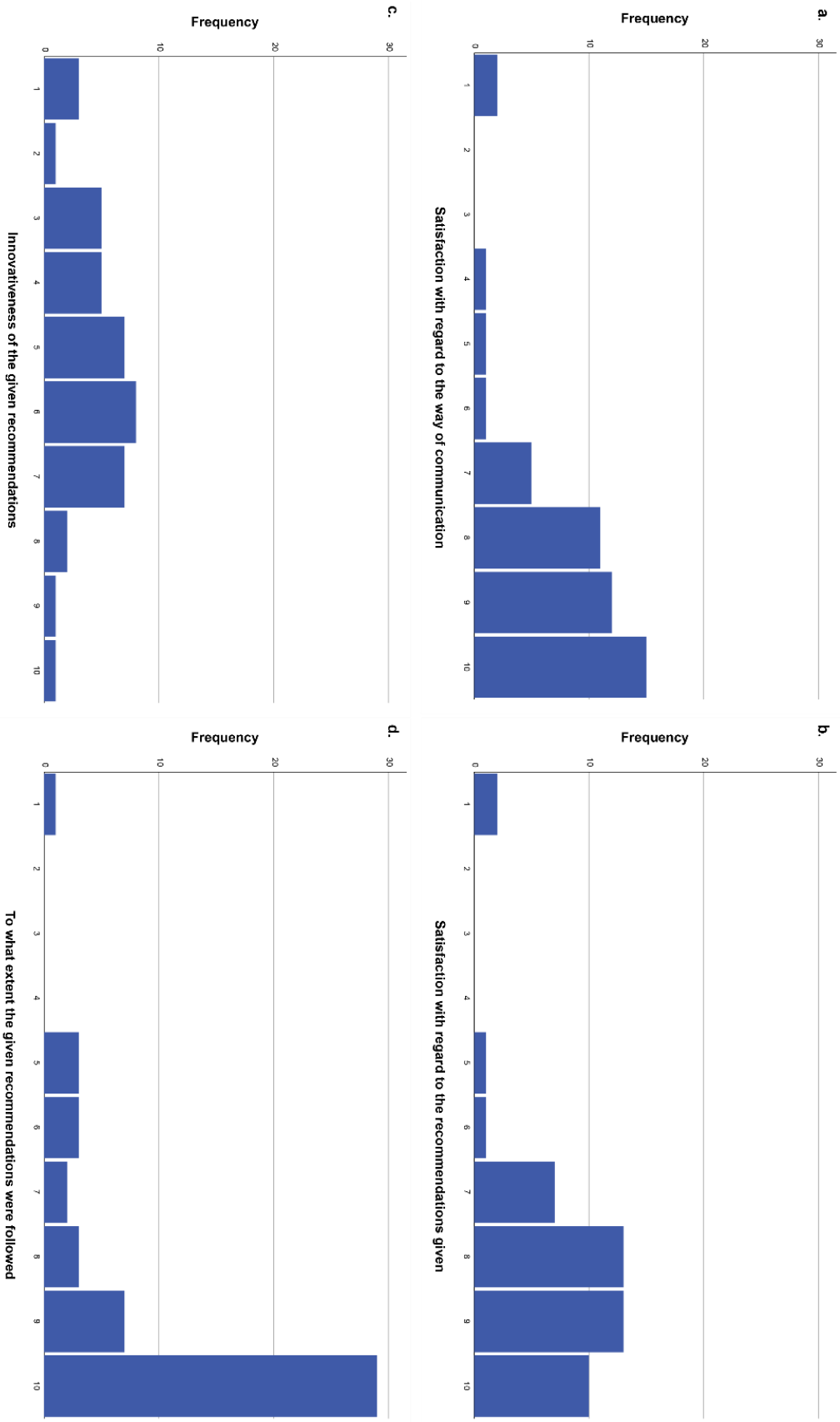
Supplementary figure 1

Overview of the hospitals requesting for recommendations in the Netherlands



Supplementary figure 2

Outcome of the questionnaire sent out to the requesting physicians. Histograms showing the satisfaction of the physicians with the different aspects of the MDT on a scale from 1 to 10. *a. satisfaction with the way of communication of the AKZ b. satisfaction with the given recommendations. c. innovativeness of recommendations, and d. adherence to the given recommendations.*



Chapter 7

Supplementary table

Overview of patients registered in the International Network on Cancer, Infertility and Pregnancy (INCIP) registry, with maternal mortality listed by country.

COUNTRY	AMOUNT OF PATIENTS IN INCIP DATABASE (%)	AMOUNT OF PATIENTS WITH MATERNAL MORTALITY
THE NETHERLANDS	491 (21%)	50
BELGIUM	471 (20%)	22
ITALY	327 (14%)	16
UNITED STATES OF AMERICA	300 (13%)	6
RUSSIA	274 (12%)	2
MEXICO	138 (6%)	13
CZECH REPUBLIC	134 (6%)	11
DENMARK	44 (2%)	1
GREECE	31 (1%)	1
POLAND	31 (1%)	2
SWITZERLAND	21 (1%)	1
SPAIN	18 (1%)	-
AUSTRIA	15 (1%)	2
GERMANY	13 (1%)	-
LITUANIA	13 (1%)	3
PORTUGAL	12 (1%)	-
ISRAEL	9 (0%)	-
GREAT BRITTAIN	5 (0%)	-
FRANCE	4 (0%)	1
CHINA	2 (0%)	-
IRELAND	2 (0%)	-
CHILI	1 (0%)	-
TUNIS	1 (0%)	-
TURKEY	1 (0%)	-
UKRAINE	1 (0%)	-

Chapter 8

Supplementary Appendix A

Search strategy Pubmed:

Concept 1 = pregnancy
Search string:
"Pregnancy"[Mesh] OR "Pregnant Women"[Mesh] OR “pregnan*”[tiab] OR “gestation*”[tiab] OR “gravid*”[tiab] OR “nulligravid*”[tiab] OR “primigravid*”[tiab] OR “multigravid*”[tiab]

⇨ 1,259,427 results

Concept 2 = sarcoma
Search string:
"Sarcoma"[Mesh] OR “sarcoma*”[tiab] OR “adenosarcoma*”[tiab] OR “carcinosarcoma*”[tiab] OR “chondrosarcoma*”[tiab] OR “fibrosarcoma*”[tiab] OR “hemangiosarcoma*”[tiab] OR “osteosarcoma*”[tiab] OR “leiomyosarcoma*”[tiab] OR “liposarcoma*”[tiab] OR “myosarcoma*”[tiab] OR “myxosarcoma*”[tiab] OR “Kaposi*”[tiab] OR “Ewing*”[tiab]

⇨ 2,348 results

Combined
Search string:
("Pregnancy"[Mesh] OR "Pregnant Women"[Mesh] OR "pregnan*"[tiab] OR "gestation*"[tiab] OR "gravid*"[tiab] OR "nulligravid*"[tiab] OR "primigravid*"[tiab] OR "multigravid*"[tiab]) AND ("Sarcoma"[Mesh] OR "sarcoma*"[tiab] OR "adenosarcoma*"[tiab] OR "carcinosarcoma*"[tiab] OR "chondrosarcoma*"[tiab] OR "fibrosarcoma*"[tiab] OR "hemangiosarcoma*"[tiab] OR "osteosarcoma*"[tiab] OR "leiomyosarcoma*"[tiab] OR "liposarcoma*"[tiab] OR "myosarcoma*"[tiab] OR "myxosarcoma*"[tiab] OR "Kaposi*"[tiab] OR "Ewing*"[tiab])

⇨ 2,348 results

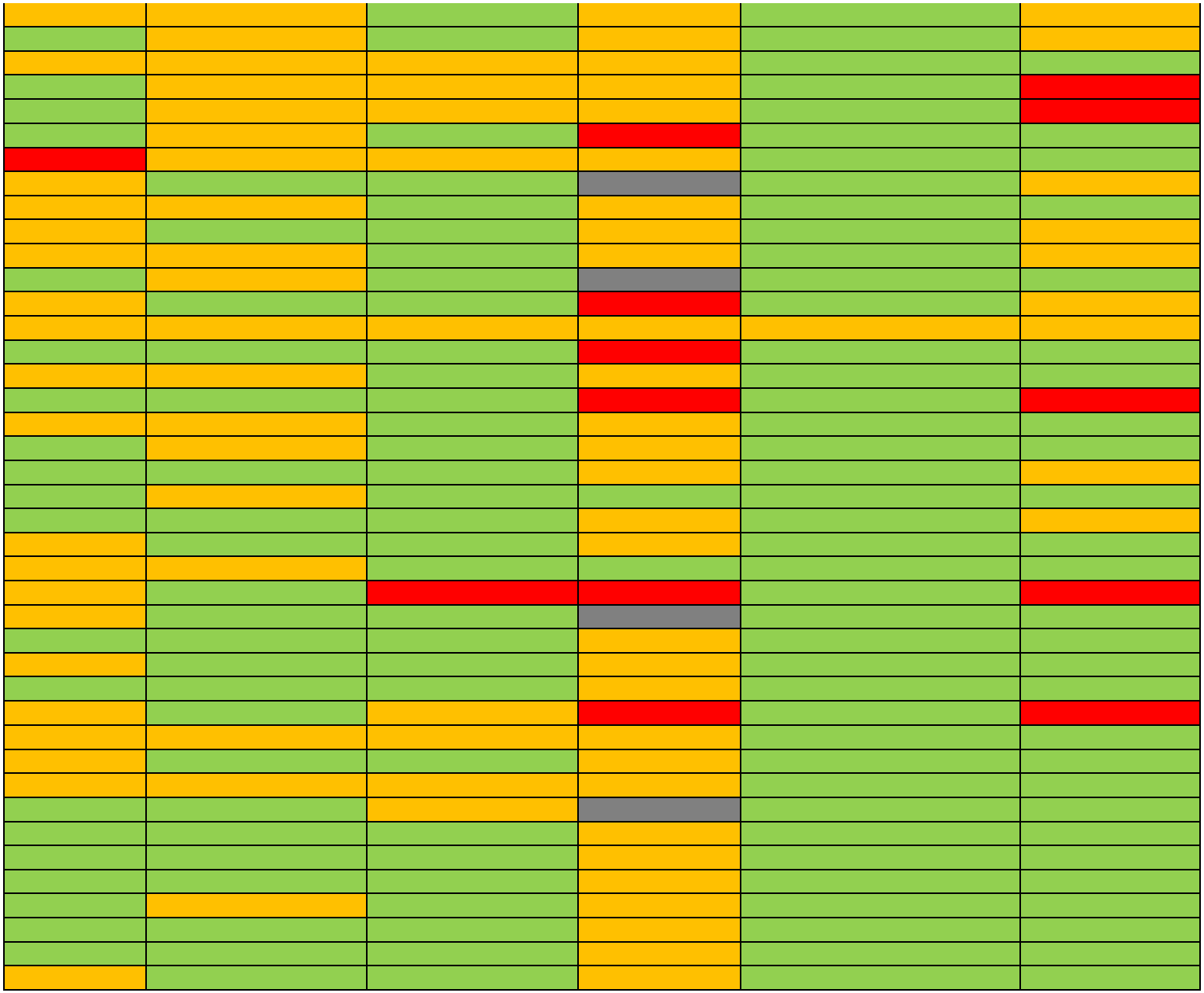
Search string:
("Pregnancy"[MeSH Terms] OR "Pregnant Women"[MeSH Terms] OR "pregnan*"[Title/Abstract] OR "gestation*"[Title/Abstract] OR "gravid*"[Title/Abstract] OR "nulligravid*"[Title/Abstract] OR "primigravid*"[Title/Abstract] OR "multigravid*"[Title/Abstract]) AND ("Sarcoma"[MeSH Terms] OR "sarcoma*"[Title/Abstract] OR "adenosarcoma*"[Title/Abstract] OR "carcinosarcoma*"[Title/Abstract] OR "chondrosarcoma*"[Title/Abstract] OR "fibrosarcoma*"[Title/Abstract] OR "hemangiosarcoma*"[Title/Abstract] OR "osteosarcoma*"[Title/Abstract] OR "leiomyosarcoma*"[Title/Abstract] OR "liposarcoma*"[Title/Abstract] OR "myosarcoma*"[Title/Abstract] OR "myxosarcoma*"[Title/Abstract] OR "kaposi*"[Title/Abstract] OR "ewing*"[Title/Abstract])) AND ((casereports[Filter] OR clinicalstudy[Filter] OR clinicaltrial[Filter] OR comment[Filter] OR observationalstudy[Filter] OR randomizedcontrolledtrial[Filter])

⇨ 804 results

Supplementary Appendix B

Scoring of all articles, based on adjusted JBI criteria. *Green = available, Orange = partly available, red = not available, grey = not applicable (for example due to termination of pregnancy / miscarriage / ongoing pregnancy)*

Author	Year of publication	1. Demographic	2. Oncological diagnosis	4. Obstetrical outcomes	6. Outcomes child	3. Treatment (during pregnancy)	5. Follow-up mother
Bernathova et al.	2005						
Scholsem et al.	2005						
Jeng et al.	2005						
Morrison & Lang	2006						
Koçak et al.	2006						
Dhanasekar et al.	2006						
Sakurai et al.	2006						
Sebitloane et al.	2006						
Sebitloane et al.	2006						
Church et al.	2006						
Cho et al.	2006						
Aboujaoude et al.	2006						
Rousková et al.	2007						
Basu et al.	2007						
Steffensen et al.	2008						
Esaka et al.	2008						
Ulker et al.	2008						
Meazza et al.	2008						
O'Brien et al.	2008						
Yaren et al.	2008						
Bertini et al.	2008						
DuBois et al.	2008						
Bodner-Adler et al.	2008						
Rai et al.	2009						
Kanazawa et al.	2009						
Lopes et al.	2009						
Fujita et al.	2009						
Hong et al.	2010						
Quaye et al.	2010						
Merced et al.	2011						
Schiavone et al.	2011						
Dueñas-García et al.	2011						
Siepermann et al.	2012						
Samadian et al.	2012						
Corrêa et al.	2012						

Adeyemo et al.	2012	
Saraiva et al.	2012	
Arikan et al.	2012	
Brunet-Possenti et al.	2013	
Brunet-Possenti et al.	2013	
Kaplan & Hoda	2013	
Reddy et al	2013	
Buchanan et al.	2013	
Arruda et al.	2014	
Patzkowski et al.	2014	
Roessler et al.	2014	
Zhang et al.	2014	
Huo et al.	2015	
Mian et al.	2015	
Bassa et al.	2015	
Oštrić et al.	2016	
Lin et al.	2016	
Wang et al.	2017	
Kudlicki et al.	2018	
Kapdagli et al.	2018	
Weidema et al.	2019	
Akhanoba et al.	2019	
Paasch et al.	2019	
Eastwood-Wilshere et al.	2019	
Wu et al.	2021	
Peng et al.	2021	
Lu et al.	2021	
Wang et al.	2021	
Li et al.	2021	
Breda et al.	2021	
Ko et al.	2022	
Zhou et al.	2021	
Bigby et al.	2006	
Wiseman et al.	2011	
Orlandi et al.	2007	
Bettendorf et al.	2006	
Azimi et al.	2006	
Bryant et al.	2004	
Di Gilio et al.	2004	
Behzatoğlu et al.	2003	
Fernandez & Kuczkowski	2003	

Said et al.	2003	
Yamamoto et al.	2003	
Yamamoto et al.	2003	
Hoshina et al.	2023	
Tachibana et al.	2015	
Aguiar Santos T.	2022	
Malalis J.F. et al.	2013	
Carsuzaa et al.	2023	
Nakajima et al.	2004	
Regmi et al.	2023	
Mahmood et al.	2023	
Pirbudak et al.	2016	
Ben-Haroush et al.	2017	
Meseci et al.	2013	
Miskovic & Dob	2013	
Mir et al.	2011	
Mir et al.	2011	
Mir et al.	2011	
Mir et al.	2011	
Mir et al.	2011	
Jiang et al.	2021	
Kowalczyk & Carr	2010	
McCarthy et al.	2007	
Akamelatu et al.	2021	
Chennouf et al.	2022	
Charo et al.	2018	
Gozukara et al.	2012	
Scherjon et al.	2009	
Stubbs et al.	2011	
Igras et al.	2012	
Goel et al.	2013	
Kellogg & Watson.	2010	
Moeckli et al.	2004	
Posma et al.	2003	
Matsuda et al.	2000	
Matsuda et al.	2000	
Jones et al.	2000	
Hashimoto et al.	2001	
Tsao et al.	2001	
Shufaro et al.	2002	
Adair et al	2001	

Supplementary Appendix C

Overview of subtypes of sarcoma

SUBTYPE OF SARCOMA; % (N)	*INCIP*	LITERATURE	ALL
LIPOSARCOMA	11.1 (5)	10.3 (12)	10.5 (17)
OSTEOSARCOMA	8.9 (4)	9.4 (11)	9.3 (15)
EWING SARCOMA	15.6 (7)	6.8 (8)	9.3 (15)
LEIOMYOSARCOMA	6.7 (3)	9.4 (11)	8.6 (14)
ANGIOSARCOMA	2.2 (1)	9.4 (11)	7.4 (12)
SYNOVIAL SARCOMA	6.7 (3)	6.0 (7)	6.2 (10)
GIST	4.4 (2)	6.0 (7)	5.6 (9)
KAPOSI'S	2.2 (1)	6.8 (8)	5.6 (9)
RHABDOMYOSARCOMA	4.4 (2)	5.1 (6)	4.9 (8)
CHONDROSARCOMA	6.7 (3)	3.4 (4)	4.3 (7)
FIBROSARCOMA	6.7 (3)	1.7 (2)	3.1 (5)
EPITHELIOID SARCOMA	0	3.4 (4)	2.5 (4)
MALIGNANT NERVE SHEATH TUMOR	2.2 (1)	2.6 (3)	2.5 (4)
UNDIFFERENTIATED EMBRYO-NAL SARCOMA	0	3.4 (4)	2.5 (4)
ALVEOLAR SOFT PART SAR-COMA	0	1.7 (2)	1.2 (2)
DERMATOFIBROSARCOMA PRO-TUBERANS	0	1.7 (2)	1.2 (2)
DESMOPLASTIC SMALL ROUND CELL	0	1.7 (2)	1.2 (2)
SPINDLE CELL SARCOMA	0	1.7 (2)	1.2 (2)
CLEAR CELL SARCOMA	0	0.9 (1)	0.6 (1)
FOLLICULAR DENDRITIC CELL SARCOMA	0	0.9 (1)	0.6 (1)
GRANULOCYTIC SARCOMA	0	0.9 (1)	0.6 (1)
HISTIOCYTIC SARCOMA	0	0.9 (1)	0.6 (1)
MALIGNANT MESENCHYMAL TUMOR	0	0.9 (1)	0.6 (1)
UNDIFFERENTIATED	22.2 (10)	5.1 (6)	9.9 (16)

Chapter 10

Supplementary table 1

Summary of case reports

Study (year)		Tumor specific information				Treatment specific information			irAE's	
	Maternal age	*Tumor type*	*BRAF mutation*	*Metastatic sites*	*LDH*	*Before pregnancy*	*At time of conception*	*During pregnancy*	*Type of irAE*	*Treatment*
Menzer (2018)	34	Melanoma	WT	Lung, pleura, lymph nodes, spine, liver, spleen	>1x ULN	NA	NA	Starting week 21: ipilimumb 3 mg/kg and nivolumab 1mg/kg	NA	NA
Mehta (2018)	31	Melanoma	V600E	ITM, subcutaneous	Unknown	Vemurafenib	Ipilimumab 3mg/kg, intralesional IL-2 9 million IU/dose	Ipilimumab 3mg/kg, intraleasional aldesleuking (IL-2) 9 million IU/dose	Grade 1 diarrhea	Third dose of ipilimumab delayed
Burotto (2018)	34	Melanoma	V600E	Breast, liver, lung, lymph nodes, bone, brain	Elevated	NA	NA	Starting week 9: ipilimumab 3mg/kg + nivolumab 1mg/kg, followed by maintenance nivolumab q3w	Liver toxicity	Corticosteroids, followed by maintenance therapy with dexamethasone and azathioprine + discontinuation of nivolumab
Xu (2019)	32	Melanoma	V600E	Lymph nodes, lung, liver	Unknown	Ipilimumab 3mg/kg, Nivolumab 1mg/kg	Nivolumab 3mg/kg	Nivolumab (3mg/kg) until week 8, ceased upon discovery of pregnancy	NA	NA
Bucheit (2020)	32	Melanoma	V600E	Breast, lymph nodes, pelvis, brain, ovary	Unknown	CVD + intralesional IL-2 + interferon, vemurafenib + combimetinib + atezlizumab	Ipilimumab 3mg/kg and nivolumab 1mg/kg	Ipilimumab 3mg/kg and nivolumab 1mg/kg following by nivolumab 3mg/kg. Last dose of nivolumab administered 7 days prior to CS	NA	NA
Haiduk (2021)	39	Melanoma	WT	Heart, lung	Normal	Nivolumab 240 mg	Nivolumab 240 mg	Nivolumab 240 mg until week 6	Suspected liver toxicity prior to pregnancy	Azathioprine prior to pregnancy
Polnaszek (2021)	23	Placental site trophoblastic tumour	NA	NA (stage I)	Unknown	Methotrexate 50mg/m^2	Pembrolizumab 200mg	Pembrolizumab 200mg q2w, discontinuation upon discovery of pregnancy before 4th dose (GA 6 2/7 weeks)	NA	NA

	Delivery	Outcomes

Study (continue)	*Gestational age*	*Modality*	*Placental involvement*	*Complications*	*Maternal*	*Fetal*
Menzer (2018)	24+2	CS	Several metastases at maternal side	No	Passed away day after giving birth	No signs of IUGR, preterm problems; 1 year FU
Mehta (2018)	Unknown	Unkown	Unknown	No	Progressive disease after delivery, switch to pembrolizumab	No physical or developmental abnormalities, no unusual infections; 2¾ year FU
Burotto (2018)	32+0	CS	Unknown	Placental insufficiency, low fetal heart rate	Partial response on vemurafenib after pregnancy	Normal developmental milestones; 11 months FU
Xu (2019)	33+0	Spontaneous premature delivery	No	IUGR	Sustained complete response at 6 months postpartum	Possible ir-thyroiditis, normal developmental milestones; 6 months FU
Bucheit (2020)	32+0	CS	No	Twin pregnancy: IUGR	1 day postpartum: generalized tonic-clonic seizure due to brain metastasis, partial response on nivolumab	NICU administration, normal developmental milestones
Haiduk (2021)	30+0	Unknown	No	Twin pregnancy: growth discordance after 24 weeks, HELLP 27 weeks	Complete remission at 9 months postpartum	Premature, one twin with missing left hand, possibly due to strangulation by amniotic cord, normal developmental milestones; 9 months FU
Polnaszek (2021)	39+4	Vaginal birth after elective induction	No	No	Remained in complete remission at 6 weeks postpartum	No follow-up information available

Caesarian section (CS); cisplatin, vinblastine, dacarbazine (CVD); follow-up (FU); Hemolysis Elevated Liver enzymes and Low Platelets (HELLP); immune-related adverse event (irAE); interleukin-2 (IL-2); international unit (IU); in-transit metastasis (ITM); intra-uterine growth restriction (IUGR); kilogram (kg); lactate dehydrogenase (LHD); milligram (mg); neonatal intensive care unit (NICU); not applicable (NA); upper limit of normal (ULN); wild type (WT).

Chapter 11

Supplementary table 1

Overview of all results from the performed diagnostic tests

	Regional hospital	UMC - First week of admission	UMC - 4 weeks after start of prednisolone	Reference values	Unit
Hematology					
Hemoglobin	7.8	6.8	4.4	6.0-8.5	mmol/L
Hematocrit	0.37	0.34	0.23	0.32-0.44	L/L
Leukocytes	13.5	14.0	11.3	5.0-17.0	x10^9/L
Neutrophils	5.11	7.61	4.29	1.5-7.5	x10^9/L
Lymphocytes	7.95	3.48	5.54	4.0-9.0	x10^9/L
Monocytes	0.4	1.96	1.02	0.2-1.6	x10^9/L
Eosinophils	< 0.1	0.23	0.34	< 0.6	x10^9/L
Basophils	< 0.1	0.03	0.11	< 0.1	x10^9/L
Thrombocytes	473	600	909	210-560	x10^9/L
Mean corpuscular volume (MCV)	77	80	78	74-94	fL
Erythrocyte sedimentation rate	n/a	1	1	n/a	mm/hr
Hemostasis					
Prothrombin time (PT)	n/a	24 (*)	n/a	n/a	sec
Activated partial thromboplastin time (APTT)	n/a	38	n/a	n/a	sec
Fibrinogen	n/a	1430	n/a	n/a	mg/L
Electrolytes					
Sodium	138	132	133	135-145	mmol/L
Potassium	n/a	5.4	4.4	3.5-4.7	mmol/L
Chloride	105	112	107	97-107	mmol/L
Calcium (ionized)	n/a	1.26	1.31	n/a	mmol/L
Phosphate	1.0	1.41	1.76	1.30-1.90	mmol/L
Magnesium	0.82	0.70	0.85	0.70-1.10	mmol/L
Biochemistry					
Creatinine	21	7	7	10.0-30.0	µmol/L
Blood urea nitrogen	<1.8	n/a	n/a	3.2-8.2	µmol/L
Alanine-aminotransferase (ALAT)	60	67	34	<45	IU/L
Gamma-glutamyltranferase (g-GT)	16	13	18	<55	IU/L
Alkaline phosphatase	191	155	189	<115	IU/L
Amylase	n/a	6	n/a	n/a	IU/L
Albumin	35	21	31	n/a	g/L
Total bilirubin	n/a	<2	<2	<17	µmol/L
C-reactive protein	<4	<1	<1	<10	g/L
Glucose	4.9	5.4	4.4	4.0-5.6	mmol/L
Lipid analysis					
Apolipoprotein B	n/a	0.49	n/a	n/a	g/L

Triglycerides	n/a	1.34	0.68	n/a	mmol/L
Total cholesterol	n/a	1.8	n/a	2.6-5.2	mmol/L
High-density lipoprotein cholesterol	n/a	0.55	n/a	>0.9	mmol/L
Low-density lipoprotein cholesterol	n/a	0.65	n/a	3.5-4.5	mmol/L
Immunology					
Immunoglobulin G	1.1	1.09	2.92	2.8-4.3	g/L
Immunoglobulin A	1.23	1.34	0.23	0.08-0.24	g/L
Immunoglobulin M	0.89	0.59	0.46	0.17-1.05	g/L
Immunoglobulin E	n/a	< 2 (**)	n/a	< 5 U/ml	g/L
anti-enterocyte IgA antibodies	n/a	Positive	n/a	Negative	
anti-enterocyte IgG antibodies	n/a	Negative	n/a	Negative	
Anti-75-kDa-antibodies	n/a	57.69	n/a	< 10	
Oxidative burst granulocyte function test	n/a	n/a	Normal	Normal	
Lymphocyte subset analysis	Normal	n/a	n/a	Normal	
Endocrinology					
Free thyroxin (fT4)	8.1	9.6	16.8	n/a	pmol/L
Thyroid-stimulating hormone (TSH)	0.99	0.67	2.15	n/a	mU/L
Parathyroid hormone (PTH)	n/a	2.6	n/a	1.7-7.7	pmol/L
Vitamins and trace elements					
Vitamin A	n/a	0.40	n/a	0.70-1.40	µmol/L
Vitamin D (25-mono-OH)	n/a	20	n/a	>50	nmol/L
Vitamin E	n/a	16.0	n/a	15-50	µmol/L
Zinc	n/a	9.0	n/a	9.3-15.1	µmol/L
Metabolic investigations					
Carnitines, amino acids and cholesterol/cholestanol	n/a	Very low citrulline levels but normal urea cycle: diarrhea-associated	n/a		
Congenital defects of glycosylation	n/a	Normal	n/a		
Feces biochemistry					
Alpha-1-antitrypsin	n/a	n/a	0.44	n/a	g/L
Elastase	78	132	>500***	>200	µg/g
Calprotectin	n/a	133	52	<50	mg/kg
Infectious diseases					
Nasopharyngeal swab PCR SARS-CoV-2	Positive	Negative	n/a	Negative	
Blood culture	n/a	Negative	n/a	Negative	
Salmonella PCR (feces)	Negative	n/a	n/a	Negative	
Shigella PCR (feces)	Negative	n/a	n/a	Negative	
Shiga-toxin producing E. coli PCR (feces)	Negative	n/a	n/a	Negative	

Campylobacter PCR (feces)	Negative	n/a	n/a	Negative	
Rotavirus PCR (feces)	Negative	n/a	n/a	Negative	
Norovirus PCR (feces)	Negative	n/a	n/a	Negative	
Astrovirus PCR (feces)	Negative	n/a	n/a	Negative	
Sapovirus PCR (feces)	Negative	n/a	n/a	Negative	
Adenovirus 40/41 PCR (feces)	Negative	n/a	n/a	Negative	
SARS-CoV-2 PCR (feces)	n/a	Negative	n/a	Negative	
Enterovirus PCR (feces)	n/a	Negative	n/a	Negative	
Parechovirus PCR (feces)	n/a	Negative	n/a	Negative	
Encephalitozoon species PCR (feces)	n/a	Negative	n/a	Negative	
Enterocytozoon bieneusie PCR (feces)	n/a	Negative	n/a	Negative	
Cystoisospora belli PCR (feces)	n/a	Negative	n/a	Negative	
Hepatitis A total Ig	n/a	n/a	Negative	Negative	
Hepatitis B s-antigen	n/a	n/a	Negative	Negative	
Hepatitis B anti-HBs	n/a	n/a	21	n/a	mIU/mL
Hepatitis B anti-HBc	n/a	n/a	Negative	Negative	
Hepatitis C serology	n/a	n/a	Negative	Negative	
QuantiFeron test	n/a	n/a	Negative	Negative	
Genetic testing					
Whole exome sequencing panel VEO-IBD/intractable diarrhea[12]	n/a	No pathogenic variant in DNA	n/a		
Pembrolizumab measurements					
ELISA heel prick card	38.6	n/a	n/a	0	µg/mL
ELISA serum	n/a	0.50	n/a	0	µg/mL

* normalized after vitamin K suppletion
** 3rd week
*** 8th week

Supplementary Appendix 1
Heel prick analysis methods.

METHODS

Determination of pembrolizumab concentration in heel prick and serum sample through ELISA.

The ELISA measurements were performed, with modifications, according to the validated method described by Pluim et al.[1] Briefly, on the day before analysis 150-fold concentrated standards were prepared from a 25 mg/mL pembrolizumab clinical stock solution (Keytruda®) in phosphate buffered saline (PBS) supplemented with 0.1% (v/v) Tween-20 and 10% (v/v) Ficoll (PBSTF10%), blank human blood and plasma in 2 mL Eppendorf® LoBind vials. Before transfer to blanc heel prick cards (Whatman™ 903 protein saver), standards were diluted 10-fold to 3,000; 1,500; 750; 300; 150; 75; 30; and 0 ng/mL in blank human blood (hematocrit of 50%), and plasma. Aliquots of 22 µL of the plasma standards and 40 µL of the blood standards were transferred to the middle of the marked circles on the heel prick cards to obtain filled spots. Next, these spiked cards were air-dried for 2 hours at ambient temperature. 4.0 mm disks were punched out in duplicate from each standard spot, while a single 4.0 mm disk was punched out from the heel prick spot. These disks were collected in separate 2 mL Lo-bind Eppendorf™ vials and 85.5 µL of PBSTF10% was added for the extraction of pembrolizumab from the punch. Subsequently, these samples were shaken in a Thermomixer™ at 1,000 rpm for 12 hours overnight at 4°C. A schematic overview of the assay can be found in Figure 1.

For the ELISA measurement, a Nunc MaxiSorp™ white 96-well flat-bottom plate was coated overnight at 4°C with 50 µL of 2 µg/mL human programmed cell death protein 1 (PD-1) (Sino Biological Inc., Beijing, China). The next day, wells were emptied and washed four times with 300 µL of PBSTF1%. The DBS extraction vials were centrifuged at 1,500g for 5 minutes, and 50 µL of supernatant from each vial was removed and transferred to the ELISA plate for analysis. Quality controls (QCs) were prepared at 80, 20, and 5 ng/mL in PBSTF10% and 20, 5, and 2 ng/mL in serum from a 25 mg/mL pembrolizumab clinical stock solution different from the stock used for the preparation of the standard curves. The 150-fold concentrated standards, prepared on the previous day, were diluted in PBSTF 10% to 200, 100, 50, 20, 10, 5, 2, and 0 ng/mL. These standards and QCs were analyzed as 50 µL duplicates per plate.
The heel prick sample was diluted 10- ,100- and 1000-fold in PBSTF10% and 50 µL of each dilution was applied to the plate.
In addition to these heel prick samples, a serum sample at time of hospital admission (19 weeks) was available and directly suitable for ELISA analysis. 50 µL was applied to the plate in duplicate. The plate was subsequently sealed and incubated for two hours at room temperature. Then, the plate was emptied and washed four times with 300 µL of PBSTF1%. After addition of 50 µL of 1 µg/mL anti-human IgG4-HRP in PBSTF1%, plates were sealed and incubated for one hour at room temperature. Next, plates were emptied and washed four times with 300 µL of PBSTF1%.
Subsequently, 100 µL of Pierce standard enhanced chemiluminescence (Pierce, Waltham, USA) was added and luminescence was measured within 15 min using a Tecan Infinite 200 Pro plate reader at 1 second per well of read time.

RESULTS

Pembrolizumab concentration in heel prick and serum sample by ELISA measurement.

The lower limit of quantification (LLOQ) for pembrolizumab in blood was 6.4 ng/mL. LLOQ was defined as the concentration that results in at least five times the relative chemiluminescence at background. The pembrolizumab recovery over the whole range of the standard curve was 33 ± 4.3% for blood, which was not significantly different from the 33 ± 1.8% recovery of pembrolizumab from plasma. Since, the standard curves for blood and plasma did not differ significantly, we conclude that 50% hematocrit did not affect the pembrolizumab determination by ELISA. However, hematocrit does affect the amount of blood absorbed per 4.0 mm DBS punch, which was 3.3 µl for plasma, 5.0 µL for blood with 30% hematocrit; 5.7 µl at 40 - 50% hematocrit; and 5.9 µl at 70% hematocrit. Therefore, the extraction of pembrolizumab with 85.5 µL of PBSTF10% results in 15-fold dilution of blood, and 27.3-fold for plasma. Unfortunately, the hematocrit level in the heel prick sample was unknown.
The concentration of pembrolizumab in the heel prick was determined in two independent assays (n=3 punches), resulting in a mean concentration of 38.6 µg/mL [range 34.7 - 41.5 µg/mL]. For both assays, an average hematocrit of 40-50% was assumed.
The concentration of pembrolizumab found in the serum sample was 0.50 [range 0.49 – 0.50] ng/mL, which was above the lower limit of detection (LOD) of 0.12 ng/mL of the ELISA method in serum. The LOD was defined as the pembrolizumab concentration that produces a signal of at least the average background plus three times the standard deviation of the background.
We found that DBS cards spiked with pembrolizumab standards could be stably stored for at least one month at ambient temperature in plastic bags with desiccant.

DISCUSSION

From these measurements, we can confirm in utero exposure to pembrolizumab. The mean concentration in the heel prick was 38.6 µg/mL, and a concentration of 0.50 ng/mL was determined in a serum sample of the child at 19 weeks.
Despite the high concentrations that were measured in the heel prick, these could be underestimated due to stability issues. The heel prick DBS cards were stored for about 2.5 years at ambient temperature and we have only proven stability of for up to one month. Since we only measure biologically active pembrolizumab with ELISA, already inactive or degraded pembrolizumab was not detected.
To improve the recovery of 33% from the heel prick DBS cards, several options were investigated. We tried the following extraction buffers: PBST without Ficoll; PBST with 1% Tween-20; PBST with 20% blank plasma; PBSTF10% at pH 6.0.

Furthermore, the following physical extraction conditions, after the addition of 85.5 µl of PBSTF10%, did not significantly influence the recovery: samples left standing still for a minimum of twelve hours at 4°C; shaking at 1000 rpm in a Thermomixer™ (Eppendorf, Bochum, Germany) for one, or twelve hours at 4°C; five minutes of sonication or one minute at medium setting in the Geno/Grinder™ (Spex Sampleprep, Metuchen, USA).
The recovery was on average only 10% ± 1% when pembrolizumab standards in PBSTF10% were spiked on Whatman™ 903 (data not shown). We believe this indicates that plasma proteins at least partly block the binding of pembrolizumab to Whatman™ 903.
Lastly, the influence of a paper disk was investigated by adding a paper disk to 5.7 µL spiked blood with extraction buffer. This resulted in a loss of around 50% of pembrolizumab, likely caused by binding to WhatmanTM 903 paper.

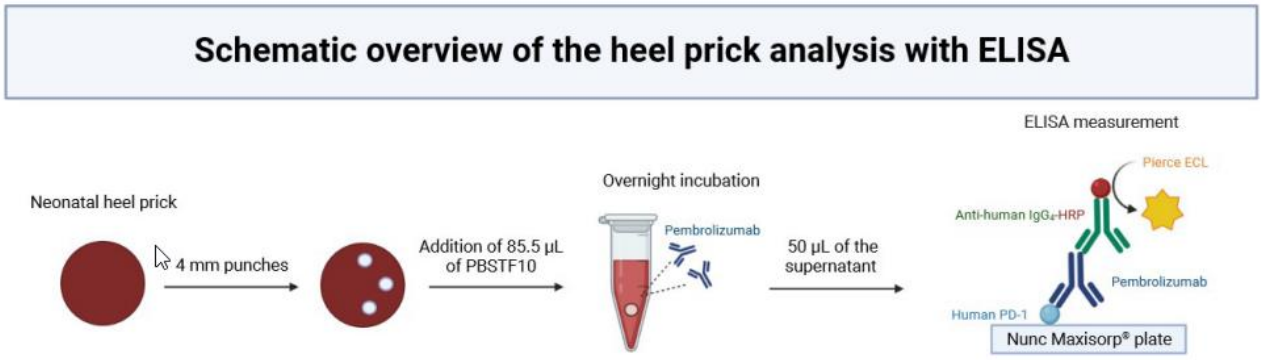


Figure 1. Schematic overview of the neonatal heel prick analysis with ELISA. To 4 mm punches of the heel prick, 85.5 µL PBSTF10 was added as extraction fluid. After overnight incubation, pembrolizumab was extracted. 50 µL of these samples were added to the Nunc 8
Maxisorp® plate. The chemoluminescence measured after performing ELISA procedure results in a pembrolizumab concentration. *This figure was made with Biorender.*

REFERENCE

1. Pluim D, Ros W, van Bussel MTJ, Brandsma D, Beijnen JH, Schellens JHM. Enzyme linked immunosorbent assay for the quantification of nivolumab and pembrolizumab in human serum and cerebrospinal fluid. *J Pharm Biomed Anal*. Feb 5;164:128-134 (2019)

Scientific acknowledgements, personal contribution, conflicts of interest and AI statement

INCIP REGISTRY

First of all, I would like to express my gratitude to all the patients and their families who agreed to have their data registered, and to the (para)medical staff who contributed to the registration of cases in the International Network of Cancer, Infertility, and Pregnancy (INCIP) database. I am also very grateful to all INCIP members for their continued international collaboration and commitment to collecting clinical data on pregnant cancer patients and their children.

With the help of **Charlotte Maggen**, **Charlotte LeJeune**, **Katrien Van Tornhout**, **Mathilde van Gerwen** and **Vera Wolters**, we have ensured that the Dutch and Belgian maternal data in the registry are kept up to date. **Indra van Assche**, **Lara Stroobandt**, **Mathilde van Gerwen** and **Evangeline Huis in 't Veld** were responsible for registering the children's data in INCIP. I was responsible for the extraction of clinical data from the participating tertiary centres in the Netherlands: the Netherlands Cancer Institute (NKI-AVL), Amsterdam University Medical Centres (AMC and VUmc sites), Radboud University Medical Centre, Erasmus Medical Centre, University Medical Centre Groningen and Catharina Hospital Eindhoven. I am grateful to the principal investigators of these centres for allowing me to review the clinical data under their supervision. In addition, I acquired missing data from the cases of the other international INCIP centres.

During this PhD trajectory, I also took on the responsibility of updating the INCIP database and transferring it to the GDPR-compliant REDcap web application of the UZ Leuven. To do this, **Indra van Assche** and I built a new database and then transferred the old INCIP database to REDCap with the help of **Jeroen Blommaert**.

ABCIP

ABCIP would not exist without the help of my (co-)promoters (**Frédéric Amant, Lia van Zuylen, Christianne Lok and Kristel Van Calsteren**). Without the knowledge of the Dutch Adviesgroep Kanker en Zwangerschap (AKZ), we would not have known where to start. Together with all the members of the AKZ we wrote standard texts and their letters of recommendation formed the basis of our work with ABCIP. I would like to thank all the **members of the AKZ** and **ABCIP**. Without their input and support, the work would not have been as comprehensive and accurate. During the course of my PhD, I was responsible for writing the draft letters of recommendation of the AKZ and ABCIP Belgium & ABCIP International. With the help of the Dutch AKZ board, **Christianne Lok, Ingrid Boere, Lia van Zuylen** and later **Ingeborg Vriens**, we were able to send a letter of recommendation within a week to all the doctors in the Netherlands who needed advice. **Frédéric Amant, Christianne Lok** and **Kristel Van Calsteren** helped me with this for ABCIP International and **Frédéric Amant** and **Kristel Van Calsteren** were responsible for ABCIP Belgium. I am very grateful to **Leonoor Coopmans** and **Anna Koning**, who are my successors for this project and who are doing a fantastic job in continuing this project.

I would like to thank **HYPE**, a web development company from Leuven, Belgium, who were responsible for the development of our website, www.ab-cip.org, without their expertise the website would not be what it is today. During my PhD I was responsible for all communication with HYPE. I would like to thank the Clinical Trial Centre and the Legal Office of the UZ Leuven for their help with the legal constitution of our website.

CHAPTER 2

Vera Wolters was responsible for the organisation of this review. All the authors contributed to writing the basis of this review. **Vera Wolters** and I worked on the first major revision of the entire review and drafted the figures. All other authors were involved in revising and approving the final version of the manuscript.

CHAPTER 4

Together with my (co-)promoters, I came up with the idea for this article and designed a questionnaire that served as the basis for this article. After collecting and analysing the data, I was responsible for the preparation, production and presentation of the published work by writing the first draft. I designed all figures. All other authors were involved in revising and approving the final version of the manuscript.

CHAPTER 5

Christianne Lok was responsible for the constitution of the AKZ and the idea for this article. Together with **Christianne Lok, Vera Wolters** and **Mathilde van Gerwen**, I kept track of all the consultation requests discussed. **Christianne Lok, Lia van Zuylen** and I**ngrid Boere** were responsible for the management of the AKZ during the writing of this manuscript. Together with my (co-)promoters, I worked on the design of the questionnaire for requesting physicians and the methodology of the article. I was responsible for collecting all the data in the database, collecting the results of the questionnaire and analysing all the data. All other authors were involved in revising the manuscript and approving the final version of the manuscript.

CHAPTER 6

Frédéric Amant was responsible for the idea of this commentary. I was responsible for writing the first draft of this commentary. All other authors participated in the revision and approval of the final version of the manuscript.

CHAPTER 7

I conceived the idea for this article together with **Lia van Zuylen** and **Frédéric Amant**. I was responsible for data collection, preparation, drafting and presentation of the published work by writing the first draft. I designed all the figures. All other authors were involved in the development of the research aims and objectives, revision of the manuscript, and approval of the final version of the manuscript.

CHAPTER 8

I was responsible for collecting all the data from the database. **Katrijn Debyser**, **Charlotte LeJeune** and I were responsible for the collection of all case reports. **Charlotte LeJeune** and I performed the most recent Pubmed search. With the help of **Katrijn Debyser**, I was responsible for writing the first draft of the manuscript. I designed all the figures. All authors were involved in the development of the research aims and objectives, revision of the manuscript and approval of the final version of the manuscript. I would like to thank **Thomas Vandendriessche, Chayenne Van Meel, Norin Hamouda** and **Krizia Tuand**, the biomedical reference librarians of the KU Leuven Libraries - 2Bergen - Learning Centre Désiré Collen (Leuven, Belgium), for their help with the systematic literature search.

CHAPTER 9

Daan Dierickx, Frédéric Amant and I conceived the idea for this review. **Daan Dierickx**, with my help, was responsible for the organisation of the review. All the authors contributed to the preparation of the basis for this review. **Daan Dierickx** and I worked on the first major revision of the review. I designed the figures. All other authors were involved in the development of the research aims and objectives, the revision of the manuscript and the approval of the final version of the manuscript.

CHAPTER 10

Frédéric Amant and I conceived the idea for this review. Together with **Jessica Borgers**, I prepared and presented the published work and wrote the first draft. I was responsible for the figures. All other authors contributed to the ideas in this review and to the formulation or development of the overall research aims and objectives. They were involved in revising the manuscript and approving the final version of the manuscript.

CHAPTER 11

After this case was discussed in the Dutch AKZ, **Frédéric Amant** and I had the idea for this important case report. We enlisted the help of **John Haanen** and **Jessica Borgers**, who were also involved in recommending the child's treating physicians, and gathered all the doctors involved to discuss the case. **Manuel Baarslag, Jessica Borgers** and I were responsible for writing the first draft. I was responsible for drafting the overview figure 1. **Nicole Gierenz** was responsible for drafting Table 1. **Manuel Baarslag** was in charge of drafting supplementary table 1. **Shoko Vos, Koen van Aerde** and **Hans Koenen** were responsible for the pathological and immunological analyses. **Pauline Buitelaar, Hilde Rosing, Jos Beijnen** and **Alwin Huitema** performed the heel prick card ELISA analyses and wrote the methods section in the appendix. All other authors contributed to the ideas in this case report and to the formulation or development of the overall research aims and objectives. They were involved in revising and approving the final version of the manuscript.

CHAPTER 12

After I registered the first case of proton therapy during pregnancy in the INCIP registry and this case was discussed by the Dutch MDAB, I had the idea to write this case report together with **Jeroen Blommaert** and **Frédéric Amant**. We gathered all the doctors involved in the UMCG. **Jeroen Blommaert, Tom Depuydt** and **Cristina Boso Martinez** made phantom models at the UZ Leuven with the help of the radiation oncology team at the UMCG. **Jeroen Blommaert** and I wrote the first draft of this manuscript. All other authors contributed to the ideas in this case report. They were involved in revising the manuscript and approving the final version of the manuscript.

Funding sources:

- Kom Op Tegen Kanker: KotK_KUL/ZKD6005 (Prof. Dr. Kristel Van Calsteren); Funding for an International advisory board on cancer in pregnancy, and neuropsychological follow-up of children prenatally exposed to (cancer) treatment
- Estée Lauder Compagnies
- Fonds AC
- The work of the INCIP was supported by :
    - The European Research Council (ERC) under the European Union's Horizon 2020 research and innovation programme '[647047 to F.A.]
    - The KWF Kankerbestrijding, the Dutch Cancer Society '[11132 to F.A.]'
    - The Fonds Wetenschappelijk Onderzoek, the Flemish Research Foundation or 'FWO' '[G0A9219N to F.A.]'.
- Prof. Dr. Frédéric Amant is senior investigator for the FWO. Research Foundation-Flanders (FWO, grant no G070514N)
- We thank the European Society Gynecologic Oncology for their continued support that enables INCIP scientific meetings.

Declaration of interests: There are no conflicts of interest to declare.

Employment:

- KU Leuven, Leuven, Belgium
- NKI/AVL, Amsterdam, the Netherlands
- Alrijne Ziekenhuis Leiderdorp, the Netherlands (since 03/2023)

Patents: None

Other financial links: None to declare

Use of Generative AI: I did not use generative AI assistance tools during the research/writing process of my thesis, except for mere language assistance

Curriculum Vitae

Joosje Heleen Heimovaara

Birth date/place: 19 september 1994, Leiderdorp, the Netherlands
Nationality: Dutch, Finnish
Adress: Bestevaerstraat 188-3, 1055TS Amsterdam, the Netherlands
Phonenumber: 06-49961196
E-mailadress: j.heimovaara@nki.nl / joosje.heimovaara@kuleuven.be
BIG-registration number: 29927312501

EDUCATION

2016 – 2020	**Msc Medicine** *Rijksuniversiteit Groningen, Groningen, The Netherlands*
2014 – 2015	**Econometrics & Operations Research** *Rijksuniversiteit Groningen, Groningen, The Netherlands* 40 ECTS in Maths, probability calculation, statistics, programming, economics and finance
2012 – 2016	**Bsc Medicine** *Rijksuniversiteit Groningen, Groningen, The Netherlands*
2006 – 2012	**Pre-university education (VWO)** *Stedelijk Gymnasium Leiden, Leiden, The Netherlands*

EMPLOYMENT

05-2024 – now	**Doctor in training Internal Medicine** *Alrijne ziekenhuis Leiderdorp, Leiderdorp, the Netherlands*
03-2023 – 05-2024	**Doctor not in training Internal Medicine** *Alrijne Ziekenhuis Leiderdorp, Leiderdorp, the Netherlands* Working as a doctor not in training for the Internal Medicine, Pulmonary medicine and Gastroenterology department and on the ER
03-2020 – now	**PhD-student 'Cancer during Pregnancy' study** *KU Leuven, Leuven, Belgium /VU Amsterdam/NKI-Av, Amsterdam, the Netherlands* The impact of an international advisory board on the management of cancer during pregnancy – promotor Professor Frédéric Amant (KU Leuven) and Professor Lia van Zuylen (VU Amsterdam)
04-2021 – 08-2021	**Doctor working for the Covid-vaccination operation** *GGD Amsterdam, Amsterdam, The Netherlands*
08-2016 – 01-2020	**Student-assistant DIPAK-consortium** *Universitair Medisch Centrum Groningen, Groningen, The Netherlands* Measuring kidney- and livervolumes on MRI scans, supporting the daily clinical student-team and supporting the labwork and analyses.

SKILLS TRAINING AND DEVELOPMENT

KU Leuven:

- **Presenting with impact**
- **Writing the PhD Dissertation: A Webinar for Graduating Doctoral Researchers**

OOA graduate school Amsterdam, The Netherlands

- **Basic Oncology course**
- **English writing course**
- **Radiation Oncology course**

Netherlands Cancer Institute, Amsterdam, The Netherlands

- **BROK certificate**

Boerhaave Nascholing, LUMC, Leiden, The Netherlands

- **Clinical Epidemiology course, Schiermonnikoog**

POSTERS & PRESENTATIONS

2020	**Advisory Board on Cancer, Infertility and Pregnancy** – Oral *INCIP teleconference, online*
2020	**International Network on Cancer, Infertility and Pregnancy** – Oral *Dutch Melanoma Treatment Registry conference, online*
2021	**Experiences of a national multidisciplinary tumor board for cancer during pregnancy in the Netherlands** – Poster *ESGO, Prague, Czech Republic*
2021	**Advisory Board on Cancer, Infertility and Pregnancy** – Poster *ESGO, Prague, Czech Republic*
2022	**Immunotherapy during pregnancy** - Oral *INCIP Meeting, Amsterdam. The Netherlands*
2022	**Immunotherapy during pregnancy** - Oral *iTOX Symposium, Paris, France*
2023	**Advisory Board on Cancer, Infertility and Pregnancy** - Oral *INCIP Meeting, Copenhagen, Denmark*
2024	**Sarcoma during Pregnancy** - Oral *INCIP Meeting, Milan, Italy*

SUPERVISION UNDERGRADUATE STUDENTS

10-2020 – 01-2021	Jessica van der Hoek **TCR T-cell treatment during pregnancy**
04-2022 – 01-2023	Katrijn Debyser **Sarcoma during pregnancy**
09-2022 – 01-2023	Michelle Methorst **Iodine-seeds during pregnancy**
10-2022 – 03-2023	Rachèl Angelier **CENSOR2**

EXTRA ACTIVITIES

04-2022	**CIP Symposium committee** *NKI-AvL Amsterdam, The Netherlands* Organization of an international two-day symposium on Cancer in Pregnancy
2021-2022	**Development of the INCIP registry database** *KU Leuven, Leuven, Belgium* Development of a large database in REDCap
2013 – 2016	**Rowing Athlete** *G.S.R. Aegir* Runner up National indoor rowing championships, 2015 Dutch National Champion 2016, W4-
2012 – 2014	**Teaching Sexual education** Providing sex education at secondary schools and organizing lectures on, for example, International Women's Day and World AIDS Day.

List of publications

- Publications used in this thesis manuscript:

1. **Heimovaara JH**, LeJeune C, Hompes D, Lok CAR, Ray-Coquard I, Van Calsteren K, van Zuylen L, Debyser K, Cardonick E, Painter RC, Witteveen EPO, Cabrera Garcia A, Shmakov RG, Amant F; International Netowrk on Cacer, Infertility and Pregnancy. Obstetric and oncological outcomes in 162 patients diagnosed with sarcoma during pregnancy: A report on cases form the International Network on Cancer, Infertility and Pregnancy and review of literature. *Submitted*
2. Dierickx D*, **Heimovaara JH***, Bellido M, Van Calsteren K, Cardonick E, Cabrera Garcia A, Baten A, Evens AM, Ferber A, Fumagalli M, Lampka E, Specht L, Vandecaveye V, Vogelius IR, Amant F. Guidelines on diagnosis and treatment of hematological malignancies. *Submitted*
3. **Heimovaara JH**, Huis In 't Veld EA, Lok CAR, Garcia AC, Halaska MJ, Boere I, Gziri MM, Fruscio R, Painter RC, Cardonick E, van den Heuvel-Eibrink MM, Masturzo B, Van Calsteren K, van Zuylen L**, Amant F**; International Network on Cancer Infertility and Pregnancy. Maternal death by cancer in pregnancy: A descriptive study of the International Network on Cancer, Infertility and Pregnancy. *BJOG*. 2024
4. **Heimovaara JH**, van Calsteren K, Lok CAR, Evens AM, Hoegl J, Ferber A, Fernandes A, Vriens I, van Zuylen L, Amant F. Results of an international survey on the current organization of care for pregnant women with cancer. *Acta Obstet Gynecol Scand*. 2024 Jan 31.
5. Baarslag MA*, **Heimovaara JH*,** Borgers JSW*, van Aerde KJ, Koenen HJPM, Smeets RL, Buitelaar PLM, Pluim D, Vos S, Henriet SSV, de Groot JWB, van Grotel M, Rosing H, Beijnen JH, Huitema ADR, Haanen JBAG, Amant F**, Gierenz N**. Severe Immune-Related Enteritis after In Utero Exposure to Pembrolizumab. *N Engl J Med*. 2023 Nov 9;389(19):1790-1796
6. Amant F, **Heimovaara JH**, Lok CAR, Van Calsteren K. The Advisory Board on Cancer, Infertility and Pregnancy: a virtual on-demand multidisciplinary tumour board. *Lancet Oncol*. 2022 Dec;23(12):1484-1486.
7. **Heimovaara JH**, Boere IA, de Haan J, van Calsteren K, Amant F, van Zuylen L, Lok CAR; Dutch Advisory Board for Cancer during Pregnancy. Ten-year experience of a national multidisciplinary tumour board for cancer and pregnancy in the Netherlands. *Eur J Cancer.* 2022 Aug;171:13-21.
8. **Heimovaara JH***, Blommaert J*, Free J, Bolt RA, Gort EM, Depuydt T, Boso Martinez C, Schoots MH, van Gerwen M, van den Heuvel-Eibrink M, Langendijk JA, Schröder CP, Amant F, Gordijn SJ, Oldehinkel E. Proton therapy of a pregnant patient with nasopharyngeal carcinoma. *Clin Transl Radiat Oncol.* 2022 May 4;35:33-36.
9. Borgers JSW*, **Heimovaara JH***, Cardonick E, Dierickx D, Lambertini M, Haanen JBAG, Amant F. Immunotherapy for cancer treatment during pregnancy. *Lancet Oncol.* 2021 Dec;22(12):e550-e561.
10. Wolters V, **Heimovaara J**, Maggen C, Cardonick E, Boere I, Lenaerts L, Amant F. Management of pregnancy in women with cancer. *Int J Gynecol Cancer.* 2021 Mar;31(3):314-322.

*shared first author
** shared last author

- Publications not used in this thesis manuscript:

1. Heesterbeek CJ, Tjan-Heijnen VCG, **Heimovaara JH**, Lenaerts L, Lok C, Vriens IJH, Van Opstal D, Boon EMJ, Sie D, de Die-Smulders CEM, Amant F, Macville MVE; Dutch NIPT Consortium. Prenatal cell-free DNA testing of women with pregnancy-associated cancer: a retrospective cross-sectional study. Lancet Reg Health Eur. 2024
2. Maggen C, Wolters VERA, Van Calsteren K, Cardonick E, Laenen A, **Heimovaara JH**, Mhallem Gziri M, Fruscio R, Duvekot JJ, Painter RC, Masturzo B, Shmakov RG, Halaska M, Berveiller P, Verheecke M, de Haan J, Gordijn SJ, Amant F; International Network on Cancer, Infertility and Pregnancy (INCIP). Impact of chemotherapy during pregnancy on fetal growth. *J Matern Fetal Neonatal Med*. 2022 Oct 6:1-11.

3. Küpers LK, Monnereau C, Sharp GC, Yousefi P, Salas LA, Ghantous A, Page CM, Reese SE, Wilcox AJ, Czamara D, Starling AP, Novoloaca A, Lent S, Roy R, Hoyo C, Breton CV, Allard C, Just AC, Bakulski KM, Holloway JW, Everson TM, Xu CJ, Huang RC, van der Plaat DA, Wielscher M, Merid SK, Ullemar V, Rezwan FI, Lahti J, van Dongen J, Langie SAS, Richardson TG, Magnus MC, Nohr EA, Xu Z, Duijts L, Zhao S, Zhang W, Plusquin M, DeMeo DL, Solomon O, **Heimovaara JH**, Jima DD, Gao L, Bustamante M, Perron P, Wright RO, Hertz-Picciotto I, Zhang H, Karagas MR, Gehring U, Marsit CJ, Beilin LJ, Vonk JM, Jarvelin MR, Bergström A, Örtqvist AK, Ewart S, Villa PM, Moore SE, Willemsen G, Standaert ARL, Håberg SE, Sørensen TIA, Taylor JA, Räikkönen K, Yang IV, Kechris K, Nawrot TS, Silver MJ, Gong YY, Richiardi L, Kogevinas M, Litonjua AA, Eskenazi B, Huen K, Mbarek H, Maguire RL, Dwyer T, Vrijheid M, Bouchard L, Baccarelli AA, Croen LA, Karmaus W, Anderson D, de Vries M, Sebert S, Kere J, Karlsson R, Arshad SH, Hämäläinen E, Routledge MN, Boomsma DI, Feinberg AP, Newschaffer CJ, Govarts E, Moisse M, Fallin MD, Melén E, Prentice AM, Kajantie E, Almqvist C, Oken E, Dabelea D, Boezen HM, Melton PE, Wright RJ, Koppelman GH, Trevisi L, Hivert MF, Sunyer J, Munthe-Kaas MC, Murphy SK, Corpeleijn E, Wiemels J, Holland N, Herceg Z, Binder EB, Davey Smith G, Jaddoe VWV, Lie RT, Nystad W, London SJ, Lawlor DA, Relton CL, Snieder H, Felix JF. Meta-analysis of epigenome-wide association studies in neonates reveals widespread differential DNA methylation associated with birthweight. *Nat Commun.* 2019 Apr 23;10(1):1893

Book chapter written not used in this thesis:

1. **Heimovaara JH**, Gordijn S, Barends C, Amant F. Principles of Gynecologic Oncology Surgery, 2nd edition: Gynecologic Oncology Surgery in the Pregnant Patient.

Dankwoord

Ik ben niet iemand die goed is in enkel individueel werken. Zonder de steun van de mensen die ik hierna zal noemen, had ik nooit zoveel kunnen bereiken in de afgelopen jaren, en dat ook nog eens met zoveel plezier. Ik wil hen hiervoor persoonlijk bedanken.

Frédéric, dankjewel dat je vanaf het eerste moment accepteerde dat deze directe Hollander haar mening gaf over jouw ideeën. Je hebt me in alles gesteund en geholpen om te bereiken wat wij samen voor ogen hadden. Daarnaast was je altijd geïnteresseerd in hoe het met mij ging, ook buiten de PhD. Bedankt dat je me de vrijheid gaf om de PhD in Leuven te combineren met mijn leven in Amsterdam, en later met mijn baan in de kliniek. Deze flexibiliteit heeft me enorm geholpen om zowel professioneel als persoonlijk te groeien.
Christianne, ik zal nooit vergeten hoe je vanaf het moment dat je me ontmoette in mij leek te geloven. Zonder jou stond ik niet waar ik nu sta. Je was kritisch, ambitieus en ondersteunend, en ik heb enorm genoten van onze overleggen waarin je me hielp mijn gedachten te structureren en aanvulde met jouw eigen inzichten. Ik hoop dat we in de toekomst nog veel mogen samenwerken.
Kristel, ondanks onze drukke agenda's wist je tijd te maken om me van frisse inzichten te voorzien en een luisterend oor te bieden. Dankjewel dat je er was wanneer ik je nodig had, en dat je vaak de cruciale puntjes op de i zette.
Lia, wat ben ik blij dat je ja zei toen ik vroeg of je mijn promotor wilde zijn. Je bent een voorbeeld voor me, met jouw kritische blik en zorgzame houding. Ik voelde me altijd vrij om mijn zorgen met je te delen en hoop net zo'n goede internist te worden als jij.

Beste prof. Lewi en prof. Wildiers. Ik wil jullie hartelijk danken voor de tijd die jullie de afgelopen jaren hebben gestoken in jullie taak als interne examencommissie. Overige leden van mijn promotiecommissie, prof. Poortmans, dr. Baas en dr. Buffart, ik waardeer de tijd die jullie hebben genomen om dit werk door te nemen met een kritische blik, en kijk uit naar de verdediging. Ik bedank ook graag prof. Topal om publieke verdediging te begeleiden.

Zonder de onderzoeksgroep van de Cancer in Pregnancy-studie in Leuven, Amsterdam en Utrecht was er nooit zoveel werk verzet. Aan alle collega's in Leuven (Marie, Katrien, Charlotte Maggen, Lara, Jeroen, Ilana, Hanne, Charlotte Lejeune, Indra, Ayaka, Rob en Carolina): dankjewel dat jullie mijn vluchtige aanwezigheid en directe meningen altijd accepteerden. Jullie hebben me enorm welkom laten voelen, en dat heb ik zeer gewaardeerd. Een extra woord van dank voor Charlotte Maggen: je hebt zoveel moeite gedaan om me in te werken en je werk aan mij over te dragen. Ik voelde me altijd gesteund door jou. Vera, Mathilde en Evangeline, ons kleine Nederlandse bolwerk: we hebben intensief samengewerkt om alles hier op gang te houden, en ik heb van elke minuut genoten. Leonoor, toeval bestaat niet, dankjewel dat je na al die jaren weer mijn pad kruiste en zo enthousiast mijn taken voor de ABCIP hebt overgenomen. En lieve Anna Koning en Charlotte Lejeune, fijn om te zien hoe goed jullie het werk voortzetten, en ik ben jullie heel dankbaar voor jullie last-minute ondersteuning de laatste weken.

Een groot deel van mijn PhD bestond uit leren van, werken voor en samenwerken met de Adviesgroep Kanker en Zwangerschap. Jullie hebben me de ruimte gegeven om te groeien, me ondersteund waar nodig en me enthousiast gemaakt voor het vakgebied. Zonder jullie harde werk had mijn project niet bestaan en had ik niet zoveel moois kunnen bereiken.

De meeste uren van mijn PhD (buiten het thuiswerken tijdens COVID) bracht ik door in het AvL. Ik kan iedere PhD-student aanraden om daar te werken, want wat een fijne plek is het! De vrijheid van de O-gang, het groepsgevoel en de georganiseerde activiteiten hebben mijn jaren extra leuk gemaakt. Extra dank aan mijn medeonderzoekers binnen de Gynaecologie: Lot, Ruby, Pien, Lianne en Marc, mijn kamergenoten Judith en Karin, en lieve Marceline. Jullie hebben naar mijn lange, niet altijd interessante verhalen geluisterd en me geholpen waar dat nodig was. Ook enorm veel dank aan de vakgroep Gynaecologie en het secretariaat, waar de deur altijd open leek te staan. En lieve Anna Koch, ik wil jou los nog even bedanken

voor de uren die we samen doorbrachten om alles wat we meemaakte de afgelopen jaren te bespreken en bij elkaar te toetsen. Ik weet zeker dat we dat nog lang vol zullen houden.

Ik wil hier graag ook mijn collega's van de Interne Geneeskunde in het Alrijne Ziekenhuis noemen. Als onwetende dokter vanuit de Gynaecologie ben ik op een plek terecht gekomen waar ik me zo gezien en gehoord voel als mezelf, dat ik niet kan uitleggen hoe dankbaar ik daarvoor ben. Jullie gaven me de ruimte om mijn promotie af te ronden naast mijn werk als ANIOS en later AIOS, en ik voelde me hierin altijd gesteund.

Buiten het professionele vakgebied wil ik mijn vrienden bedanken die me al die tijd hebben bijgestaan. Ik wil er een paar specifiek noemen. Lieve Anne Mieke, Machteld, Hà, Iza en Donna, jullie staan al meer dan 15 jaar aan mijn zijde. Jullie vriendschap heeft me rust gegeven en ik waardeer dat enorm. Iz, je begrijpt me altijd, Machteld, je staat altijd voor me klaar, Hà, ik weet al jaren dat ik altijd bij je terecht kan, en Miek, je bent en blijft mijn rots in de branding. Lot en Joos, de bijzondere vriendschap die we hebben is er een die me basis geeft. Jullie hebben me gesteund in mijn dieptepunten en de hoogtepunten steeds met me gevierd.

En dan de mannen die de afgelopen vier jaar altijd voor me klaar stonden, lieve Bas, Evert, Julius, Kevin, Melle, Thijs en Timothy. Jullie hebben me de afgelopen jaren tijdens dit proces gesteund, me laten uitrazen als het nodig was en me meegesleurd naar leuke dingen als ik daar duidelijk aan toe was. Wat voel ik me een rijk mens met de jullie vriendschap.

Lieve familie. Ik besef me maar al te goed hoe bevoorrecht ik met jullie ben. Lieve Heimovaara's. Elk van jullie is ambitieus, houdt ervan zijn best te doen en kijkt om naar de mensen om hen heen. En dat met een grote dosis luchtigheid en een voorliefde voor het bourgondische leven. Door jullie is makkelijk om te zien dat hard werken en een fijn privéleven hand in hand kunnen gaan. Lieve Dijkstra's, ik vind het bijzonder hoe hecht onze band is. Met zoveel dokters in de familie is het niet gek om dit pad te volgen, maar alle voorbeelden en adviezen hebben me de afgelopen jaren enorm geholpen en gesteund in mijn keuzes. Onze vriendschappen, het warme samenzijn en het luisterende oor wat er altijd is koester ik.

Aan mijn bonus familie, de familie van Duijn: Een extra gezin, zo anders zijn dat je eigen familie, maakt een mens enorm rijk. Bert, ik hoop dat ik je teleurstelling (geen wetenschappelijke studie doen maar geneeskunde) een beetje goed heb gemaakt door deze PhD. Grapje natuurlijk, maar dank voor je voortdurende steun en enthousiasme in alles wat ik doe. Mei, ik voel me altijd zo gezien en geliefd door je. Julia, je rust en openheid blijft me inspireren het beste uit mezelf te halen en Anna, het is zo bijzonder om iemand naast je te hebben staan die alle stappen in je leven heeft gevolgd en precies weet wie je bent, dankjewel voor de afgelopen 30 jaar.

Fenneke en Dautse, in stilte aanwezig bij alles wat ik doe, altijd daar als ik mijn hart wil luchten en altijd in voor een knuffel (ook als ik het niet accepteer). Ik besef me maar vaak hoe blij ik ben dat ik jullie als zusjes heb. En tot slot, lieve Pap en mam. Jullie hebben me geleerd mezelf te blijven en hebben me altijd gesteund. Jullie zijn zo'n groot voorbeeld voor mij, hoe jullie werk en gezin hebben gecombineerd, er echt altijd voor ons waren (en nog zijn) en nu staan waar jullie staan. Dankzij jullie ben ik trots op wie ik nu ben.