Cancer and Pregnancy

de Haan, J.

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CHAPTER 1

General introduction

EPIDEMIOLOGY

The incidence of cancer during pregnancy is approximately 1 in 500-1000 pregnancies in the Western world.[1,2] Women delay childbearing until their thirties and forties and with increasing age, the overall risk of cancer will also increase. As a consequence, the occurrence of cancer during pregnancy is increasing.[3] However, the increasing incidence from 112 patients per 100 000 pregnancies in 1994 to 192 patients per 100 000 pregnancies in 2008, cannot be explained completely by increasing age.[2] Also, increased awareness of the possibility of cancer in pregnancy, better diagnostic possibilities during pregnancy or other yet unknown factors contribute to this increase.[2]

Malignancies developing during pregnancy are not different from those in non-pregnant women with the similar age. Breast cancer, haematological cancer, cervical cancer, ovarian cancer and invasive skin cancer are the most frequent malignancies diagnosed during pregnancy (Figure 1). Large population based studies found that pregnancy itself is not a risk factor to develop a malignancy.[4] However, it has been suggested that a delay in diagnosis and treatment is present in pregnant cancer patients due to overlapping symptoms of physiologic changes in pregnancy and little awareness about the possibility of cancer during pregnancy.[5]

ONCOLOGICAL MANAGEMENT IN PREGNANCY

Diagnosis

Diagnosing cancer without delay is as important in pregnant patients as in non-pregnant patients. Preferably, the same imaging modalities as advised in the regular guidelines are used in order to avoid a suboptimal diagnostic process. However, the maternal benefits and potential fetal risks should be balanced. Both non-ionizing and most ionizing imaging modalities are safe and accurate during pregnancy and valuable information on the type or stage of disease can be obtained.[6-8] The amount of fetal exposure to ionizing techniques should be kept as low as reasonably achievable and if non-ionizing imaging alternatives with equal accuracy are available, they should be preferred. The cumulative fetal radiation exposure of all expected ionizing techniques performed during pregnancy should be determined at the beginning of treatment. The calculated maximum exposure should be below 100 mGy. Past this threshold, the chance of congenital malformations and childhood cancer rises above 1%.[9,10]

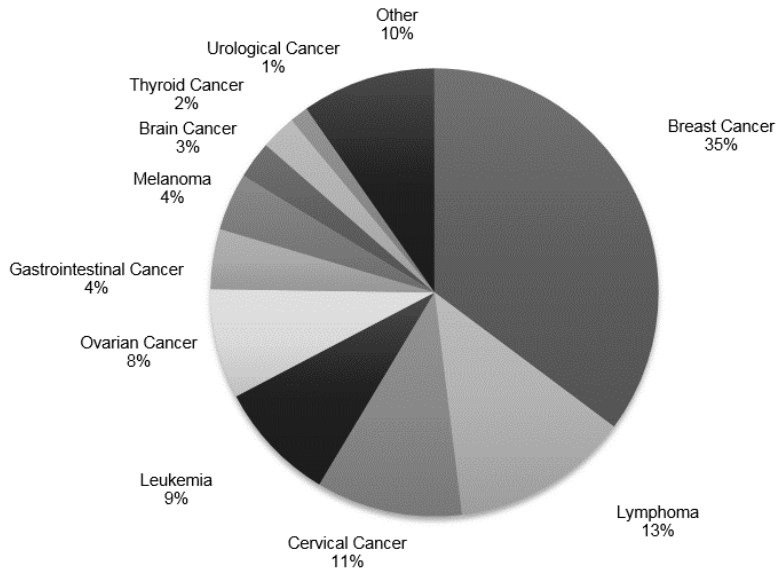

Figure 1. Distribution of malignancies during pregnancy from the INCIP registration study, accessed on 08-2018.

Therapy

Pregnant cancer patients should be treated in an experienced multidisciplinary team. This team should at least include oncological specialists (depending on the malignancy), obstetricians/perinatologists, neonatologist, radiotherapists and psychologists in order to provide optimal care for both mother and child. It depends on the type of malignancy, the stage of disease and the preferences of the patient after counselling, whether the pregnancy can be continued without hampering maternal or fetal outcome.[4] Independent of whether or not the pregnancy is continued, it is always advised to treat the patient like non-pregnant patients according to the standard protocol as much as possible.[11-13]

Non-obstetrical surgery in pregnant women has proven to be safe for the foetus as long as maternal parameters, including blood pressure and oxygenation are stable. In case of abdominal surgery, extra precaution must be taken to avoid manipulation of the uterus to minimize the chance of premature contractions. In case of laparoscopy, an open introduction is preferred above blind insertion of the Veress needle to avoid perforation of the uterus and intra-abdominal pressure should be kept low and the procedure should be limited in time.[11,14,15]

Chemotherapy during pregnancy has been controversial for years due to the toxic effect of chemotherapy in the human body and placental transfer to the fetus. In baboon models, transplacental transfer of different chemotherapeutic agents ranged from 60% transfer of carboplatin to only 2% transfer of taxanes (Table 1).[16,17]

Table 1. Transplacental transfer of chemotherapeutic agents.[16,17]

Chemotherapeutic agent	Placental transfer
Carboplatin	± 60%
Cyclophosphamide*	± 20%
Antracyclines	< 10%
Taxanes	< 2%
Vinca alkaloids	± 20%

* Active metabolite, % in fetal circulation of concentration in maternal circulation.

The effect of in utero exposure to chemotherapy in humans has been evaluated by several studies. The teratogenic effect of chemotherapy depends on the type, amount and threshold dose of the chemotherapy and the stage of fetal development. The teratogenic effect is more extensive during organogenesis in the first trimester, especially in early first trimester (Figure 2).[18] Cohort studies on the effect of antenatal chemotherapy exposure in the second and third trimester of pregnancy show reassuring results on the neonatal and infant outcome with a follow up until three years strengthening the idea that oncological treatment in pregnancy is feasible.[19] However, increased risk on adverse obstetric outcome like congenital malformations when given in the first trimester and preterm delivery and small for gestational age neonates have been described by some studies.[20-24] Increased preterm delivery rates were mainly due to iatrogenic preterm delivery, when, due to the unknown effect of antenatal chemotherapy exposure, labour was induced preterm to start treatment postpartum.[2,20,22,25,26] Restricted fetal growth, leading to small for gestational age neonates, in patients exposed to chemotherapy during pregnancy, is thought to be caused by the negative effect of chemotherapy on rapidly growing cells in the placenta leading to increased oxidative DNA damage and impaired placenta growth and development.[27] Also maternal malnutrition, high stress levels and administration of supportive drugs including anaesthetics and anti-emetics could attribute to the observed fetal growth restriction.[28-30]

For radiotherapy during pregnancy, the same cumulative safety threshold as for ionizing imaging techniques of 100 mGy applies. Fetal radiation exposure during pregnancy depends on the radiation field, radiation dose and gestational age. Negative effects of radiation can

be divided in deterministic and stochastic effects. Deterministic effects are effects that occur when a threshold is crossed.[10,31]

High fetal radiation exposure during organogenesis will lead to congenital malformations, while later in pregnancy, intrauterine growth restriction, mental impairment or intrauterine fetal death can be expected. Stochastic effects are unforeseen effects that can occur years after exposure and are therefore difficult to predict. Stochastic effects of fetal radiation described in literature include an increased chance of paediatric cancer after exposure exceeding 100 mGy (3-4 per 1000 children).[10] Before the start of radiotherapeutic treatment of pregnant patients, models should be used to calculate the expected cumulative fetal radiation during treatment in order to balance the maternal benefits and the fetal risks.

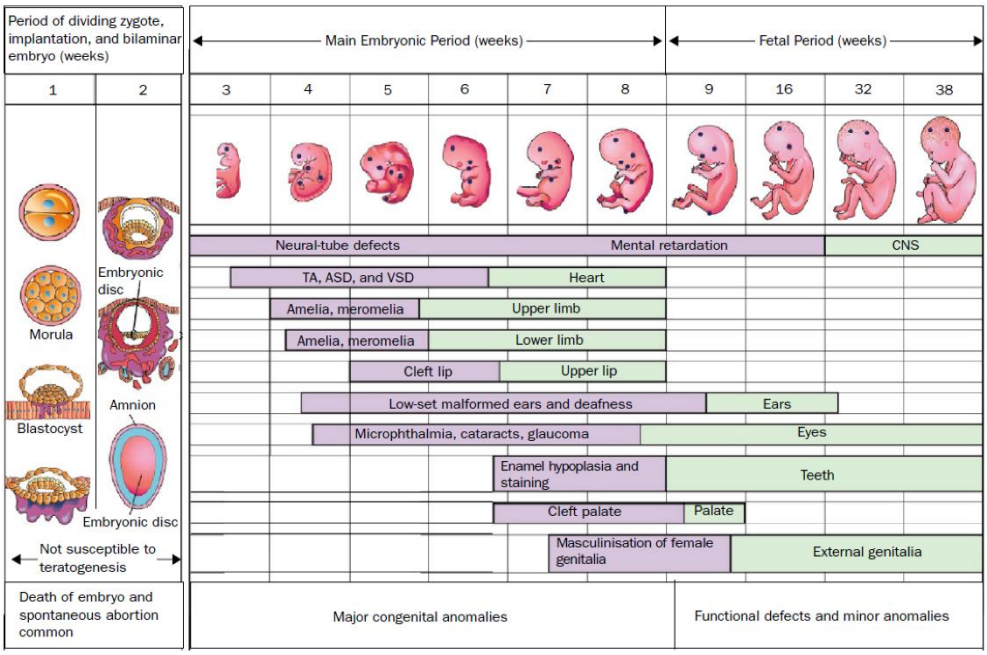

Figure 2. Crucial periods in prenatal development. Horizontal bars indicate fetal development during a highly sensitive period (purple) and a less sensitive period (green). TA, truncus arteriosus; ASD, atrial septal defect; VSD, ventricular septal defect. Reproduced with permission from Moore P. ed. The developing human, 8th edition, 2008.

The field of immune therapies and target therapies is rapidly growing, providing cancer patients with new possible treatment strategies. Literature on the effect of immune therapies and targeted therapies in pregnancy is scarce. Targeted agents have a different structure, metabolism and pharmacokinetics compared to chemotherapy. Therefore, a

different pattern of adverse effects and safety of mother and child should be anticipated. The majority of targeted agents are small molecules that can cross the placenta easily. Others agents are large monoclonal antibodies that reach the fetus through a transporting system in the placenta. For most of targeted agents, the known effect is investigated in rodent models or case reports only. Based on this information, these new agents cross the placenta and can have a (theoretical) negative effect on pregnancy depending on the type of therapy.[32,33]

In the last two decades, literature on the effects of cancer on maternal and pregnancy outcome and maternal and fetal safety of therapy during pregnancy has been published. Before 2013, healthcare professionals often advised to terminate pregnancy after a cancer diagnosis in the first trimester or to induce delivery preterm in order to start immediate treatment.[34] This resulted in a high termination of pregnancy rate [20,24-26,35-38] or iatrogenic (extreme) prematurity rate.[19-21,25,26,35,39-41] If pregnancy was continued, therapy was often postponed until after delivery, providing substandard and delayed therapy to the patient with possibly a worse outcome. Due to the increasing interest in cancer in pregnancy and the increasing incidence, care for these women and their unborn children has changed. However, studies on the possible adverse outcomes like preterm delivery and small for gestational age neonates were hampered by small cohort sizes and focused on only small subgroups. Therefore, it was not yet possible to define specific patients at risk for poor outcome.

INTERNATIONAL NETWORK ON CANCER, INFERTILITY AND PREGNANCY (INCIP)

Due to the relative rare occurrence of cancer in pregnancy and the heterogenic population , the only option to evaluate possible care and outcomes is to obtain data from multiple international centres. In 2005, a lack of large cohorts studies on cancer in pregnancy led to the establishment of the registration study on cancer in pregnancy in Leuven, Belgium. With expansion of the registration study on an international level and the growing number of participants, an international taskforce on Cancer in Pregnancy was founded and after joining forces with specialists on fertility preservation, the International network on Cancer, Infertility and Pregnancy (INCIP) was established. The importance of this network was acknowledged by the European Society of Gynaecological Oncology (ESGO), and INCIP was embraced as a network. The primary objective of INCIP was to register patients with cancer in pregnancy both retrospectively and prospectively to increase knowledge on the care for pregnant cancer patients, including data concerning demographic and oncological characteristics, diagnostics and providing treatment and obstetric and maternal outcome.

AIMS AND OUTLINE OF THIS THESIS

Aim

In this thesis we aimed to identify difficulties in diagnosis of cancer in pregnancy and possibilities to improve these difficulties. Also, we aim to analyse risk factors for adverse outcome, changes in care and outcome over time and treatment and outcome of specific malignancies. The thesis is divided in three parts:

Part I: Difficulties and delay in diagnosis

In this part, we aim to elucidate the difficulties in the diagnostic management in pregnant patients with cancer and the possibilities to overcome these difficulties. **Chapter 2** describes a review of the literature on the difficulties of diagnostics in pregnant patients with cancer. The diagnostic process from presentation of symptoms, safety and feasibility of interventions, to pitfalls in the interpretation of these interventions, is summarized. In **chapter 3**, we analyse a subgroup of cancer related maternal mortality cases from the Dutch Maternal Mortality committee. From these cases, the cause and extend of delay in diagnosis and therapy was assessed in order to evaluate if we can improve care of avoid this unfortunate situation.

Part II: Cancer in pregnancy: an international registration study

Part II describes several analysis based on data from the INCIP registration study. In **chapter 4** we describe an analysis of the largest cohort of patients with cancer in pregnancy. We evaluate changes in oncological management and obstetric and neonatal outcome over 20 years. In addition we analyse the management, oncological and obstetric outcomes of two rare malignancies during pregnancy; colorectal cancer during pregnancy in **chapter 5** and thyroid cancer during pregnancy in **chapter 6**.

Part III: Melanoma, pregnancy and fertility

In part III we question several clinical issues on melanoma and pregnancy. In **chapter 7** we evaluate the maternal and obstetric outcomes of 60 pregnancies complicated by both primary and recurrent melanoma. In **chapter 8** we describe a case of a pregnant patient with metastatic melanoma and a severe adverse reaction to vemurafenib during pregnancy leading to adverse obstetric and neonatal outcome. In the care for young female melanoma patients, fertility and pregnancy are items that play an important role. Previous literature suggested that melanomas are susceptive to hormones and literature on the effect of pregnancy and artificial reproductive therapies on prognosis are conflicting. In **chapter 9** we

describe the results of a questionnaire study among all fertile female melanoma patients from the Antoni van Leeuwenhoek hospital to assess the use of assisted reproductive technology (ART), the number of pregnancies and recurrences of melanoma in this group to determine the sample size and feasibility of a nationwide study and to gather some preliminary data on chance of recurrence of recurrence after pregnancy or ART.
The general discussion and recommendations for further research are presented in **chapter 10**.

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