Cancer and Pregnancy

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SUMMARY

In this thesis, we evaluate the development of oncological and obstetrical management in women with cancer during pregnancy in the last 20 years. In **chapter 1**, a general introduction of the subject and the research aims are described. We aim to identify pitfalls and risks for adverse outcome that healthcare professionals can be confronted with when providing care for these patients and their unborn children and how to avoid them. Our research is mainly based on the international registration study of the 'International Network on Cancer, Infertility and Pregnancy' (INCIP).

PART I DIFFICULTIES AND DELAY IN DIAGNOSIS

In part I of this thesis we describe the occurrence and extent of delay in diagnosis and treatment of cancer during pregnancy. We elaborate on the difficulties and possibilities of diagnostics during pregnancy. Even though cancer during pregnancy is relatively rare, delay may lead to more (earlier) maternal mortality. In **chapter 2** we evaluate the prevalence of cancer related maternal mortality in the Netherlands using the database of the Dutch Maternal Mortality Committee. This resulted in a cancer related maternal mortality rate of 1.23 per 100,000 live births. Each medical history was assessed by ten medical specialists with clinical experience in the care for pregnant cancer patients. They individually scored the cases on the presence of delay in diagnosis or treatment and whether this delay was patient- or doctor related. In 65% of the patients delay was present, most often a delay in diagnosis. The majority of this delay was caused by healthcare professionals. Avoiding delay in diagnosis and therapy in patients with pregnancy related cancer could potentially improve maternal and neonatal outcome. It is therefore essential to increase awareness among health care providers about the occurrence and recurrence of cancer in pregnancy and the possibilities of diagnostic and therapeutic interventions in these women. The diagnostic pitfalls of cancer during pregnancy and the possibilities to improve them are described in **chapter 3**. Diagnosis and staging of cancer during pregnancy may be difficult due to overlap in physical signs of malignancy and physiological pregnancy changes and limited knowledge on the safety and accuracy of diagnostic tests. Tumour markers should be used with caution due to pregnancy-induced elevation of some. Markers like Inhibin B, anti-Müllarian hormone (AMH), human epididymis protein 4 (HE4), lactate dehydrogenase (LDH), CA 19-9 and carcino-embryonic antigen (CEA) are not elevated by pregnancy, and can be used as in the non-pregnant population. When using imaging in pregnant patients, fetal exposure to radiation must always be kept in mind and when possible, non-ionizing techniques are preferred. If the use of ionizing imaging and staging techniques are preferred

for better diagnostic accuracy, cumulative fetal radiation exposure must be calculated and should remain below 100 mGy during the entire pregnancy. Exposure above 100 mGy increases the risk of congenital malformations or mental retardation. The exact exposure depends on the area of radiation, the amount of radiation and the gestational age and can be calculated by using special models. Ionizing imaging techniques can increasingly be avoided with the technical devolvement of non-ionizing techniques such as magnetic resonance imaging (MRI), including whole body MRI and diffusion-weighted imaging, which potentially hold great opportunities for the diagnostic management of pregnant cancer patients. The use of radioactive labelled markers like techneticum-99 during a sentinel node procedure or 2-deoxy-2-[fluorine-18]fluoro-D-glucose (^{18}F-FDG) during positron emission tomography (PET) scans appear to be safe during pregnancy but long term follow-up is lacking. Pathological evaluation and establishing a diagnosis of malignancy can also be difficult in pregnant women as physiological changes can mimic pathology of some malignancies resulting in false positive results. Therefore, the pathologist should always be informed about the pregnant status of the patient. In the diagnostic process, availability of techniques and experience are needed to avoid delay in the diagnosis.

PART II CANCER IN PREGNANCY: AN INTERNATIONAL REGISTRATION STUDY

Part 2 reports on the results of the international registration study of the INCIP. **Chapter 4** describes the largest cohort published on cancer in pregnancy and includes 1170 women with a primary malignancy during pregnancy. This study describes the oncological management and obstetric and neonatal outcomes of patients registered in INCIP and treated in the past 20 years, and assesses associations between cancer type or treatment modality and obstetric and neonatal outcomes. We evaluate the most common adverse outcomes like preterm prelabour rupture of membranes or preterm contractions, a birthweight being small for gestational age (below the 10th percentile) or admission to a neonatal intensive care unit (NICU). Breast cancer was the most common malignant disease (39%). Of all 1170 patients, 779 (67%) received treatment during pregnancy. Eighty-eight percent of all singleton pregnancies ended in a livebirth, of which 48% ended preterm. A negative association was found between exposure to platinum-based chemotherapy and small for gestational age and between taxane chemotherapy and NICU admission. NICU admission depended also on malignancy type, with gastrointestinal malignancies having highest risk and thyroid malignancies having lowest risk. Other associations between treatment or malignancy type and outcomes were less clear. During the study period

between 1996 and 2016, every 5 years, the likelihood of receiving treatment during pregnancy increased with 10%, mainly related to an increase of chemotherapeutic treatment (31% every 5 years). Each 5 years, we observed 4% more livebirths and 9% fewer iatrogenic preterm deliveries.

In **chapter 5**, we describe a subgroup analysis on 27 pregnant patients with colon carcinoma and 14 pregnant patients with rectal carcinoma. Colorectal carcinoma during pregnancy is rare, with an incidence of 0.8 per 100,000 pregnancies. Advanced disease was present in 73% of these patients. During pregnancy, 51% received surgery and 29% received chemotherapy. Pregnancy ended in 81% with a live birth, most of which were premature (79%). Eight babies were small for gestational age (28%). Overall 2-year maternal survival was 64% which is a similar prognosis compared with the general population. A subgroup analysis on 35 pregnant patients with thyroid cancer is described in **chapter 6**. Thyroid cancer, occurring in 3% of the women included in our cohort, and has been reported to occur in up to 10% of all pregnant cancer patients, is less rare than colorectal cancer. In the group of young female thyroid cancer patients, the majority of tumours are well-differentiated and are therefore almost always diagnosed in stage I. Its treatment poses a risk for the pregnancy, as the thyroid gland plays a crucial role in the evolution of pregnancy. Of our patients, 83% underwent surgery during pregnancy, mainly total thyroidectomies. The median number of days between diagnosis and surgical treatment was significantly different between the groups with surgery during and after pregnancy (27 vs. 139 days) but the clinical impact of this difference is due to the small number of patients unknown. Both maternal and neonatal outcomes were good. In the Letter to the Editor, published in **appendix 2**, the current situation of the registration study and the need for international collaboration is once more emphasized.

PART III MELANOMA, PREGNANCY AND FERTILITY

In part 3, we specifically describe a group of women with melanoma during pregnancy as melanoma is one of the most common cancers diagnosed during pregnancy. Especially in the patients with advanced stage disease during pregnancy creates difficulties in the treatment as particularly these patients might benefit from the rapidly growing number of new treatment options, that are not yet investigated during pregnancy. Also, we elaborate on the possible negative effects of pregnancy and assisted reproductive technologies on recurrence after a primary diagnosis of melanoma during the fertile years. In **chapter 7** we give an overview of 60 women with melanoma during pregnancy. Half of them had stage III (n=14, 23%) or stage IV (n=16, 27%) disease at diagnosis and 27% presented with

recurrent disease during pregnancy. Surgery was the main therapeutic strategy during pregnancy, only four patients with advanced melanoma were treated during pregnancy with systemic therapy (n=1) or radiotherapy (n=3). Premature delivery was observed in 18% of the ongoing pregnancies, all which were iatrogenic and in 78% of the premature deliveries it concerned patients with advanced melanoma. Five years maternal survival was 61%. It is known that only a limited response to chemo- or radiotherapy can be expected in these melanoma patients. New immune- or targeted therapies are promising and are more and more indicated in non-pregnant women with melanoma. The use of these new therapies during pregnancy is experimental since the limited number of articles published. The limited number of case reports published show conflicting results and based on animal studies or the working mechanism of these therapies, negative effects on the pregnancy could be expected for some of these treatments. It is also important to take into account the possible maternal adverse reactions**. Chapter 8** describes a case report of a pregnant patient with stage IV melanoma during a twin pregnancy. She started treatment at 22 weeks of gestation with vemurafenib. No direct obstetrical adverse reactions were described, considering fetal growth and general condition. However, treatment was complicated by toxic epidermal necrolysis, a severe maternal adverse reaction of the skin, resulting in spontaneous preterm delivery at a gestational age of 26 weeks. The patient died shortly after due to progressive disease.

Melanoma is one of the most common cancers in fertile women. In the last years, the effect of hormones on the occurrence and progression of melanoma has been matter of debate. Recent reviews show no negative effect of pregnancy and hormonal contraceptives on the first diagnosis of melanoma and also women with melanoma during pregnancy do not seem to have a worse outcome than non-pregnant melanoma patients. In 2012, an Australian study showed a negative association between IVF and ongoing pregnancy and the primary diagnosis of melanoma. However, the effect on recurrence in women with a melanoma in the medical history was still unknown. In **chapter 9** we describe the results of a pilot study using a questionnaire among fertile women with a history of melanoma. We aimed to establish the use of assisted reproductive technology (ART) and pregnancy after a history of melanoma and the effect on recurrence of melanoma. Response rate was 49%. Of the 354 answered questionnaires, 309 were from living women and 45 of relatives of diseased women. The majority of women (n=218, 63%) had a history of stage I primary disease. In total, 38% of the women became pregnant after their melanoma diagnosis. Only 17 women (5%) conceived after using ART. There was no difference in recurrence rate between women who had ever been pregnant and those who had never been pregnant. Due to the

low number of ART after primary melanoma, it was not possible to evaluate the effect of ART on recurrent melanoma. Registration of these women, including follow-up on fertility related information, will provide more information on the possible increasing incidence of ART and recurrent melanoma in the future. This will be very helpful for preconceptional counselling of these women.

In the general discussion, **chapter 10**, we discuss the past, present and future of cancer in pregnancy based on results from this thesis. While a lot of changes has already been made in the care for pregnant patients in the last years, many are still to come. With increasing knowledge and reassuring results, we must not forget the complexity of cancer in pregnancy. It describes a heterogenic group of patients, with few exposures per year per hospital, especially for the less common malignancy types, and an urgent need for individualized care in these patients based on malignancy type, stage of disease, gestational age and individual preferences of the patients after counselling. Centralisation of care in several specialized hospitals is necessary to meet the requirements of multidisciplinary, individual patient made treatment to optimize maternal and neonatal outcome. Further collaboration on an international level, mandatory registration of these patients, establishment of national and international advisory boards and active participation of patients will further aid in providing our patients with the best possible knowledge for optimal counselling and to provide the best possible care.