Update on cancer in pregnancy

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SUMMARY

The association of cancer with pregnancy is rare, but a rising incidence is expected because of the increasing maternal age at first pregnancy. A cancer diagnosis during pregnancy reveals several medical and ethical dilemmas because diagnostic procedures and treatments may compromise foetal health. But on the other hand, delay in diagnosis and treatment should be prevented since this can adversely affect maternal outcome. There are no data suggesting that the termination of pregnancy improves the prognosis and the awareness of the feasibility of cancer treatment during pregnancy is growing. The oncological and obstetrical management of a patient that is diagnosed with cancer during pregnancy requires a multidisciplinary approach, taking the patient's perspective into account. This review summarises the current knowledge on incidence, diagnosis, treatment, prognosis, obstetrical and neonatal outcome of cancer during pregnancy.

(BELG J MED ONCOL 2018;12(7):319-325)

INTRODUCTION

The incidence of cancer in pregnancy is rare. The management of these patients is challenging because two persons with conflicting interests are involved. The mother needs cancer treatment that may harm foetal health. Because of socio-economic reasons, more women delay childbirth and the overall maternal age is increasing. As the incidence of cancer increases with age, it is expected that more women will be diagnosed with cancer during pregnancy. In the past, termination of pregnancy or delaying treatment until postpartum were the advised options, based on fear for the potential toxic effect of cytotoxic treatment on the unborn child. This resulted in the loss of wanted pregnancies and impairment of the maternal prognosis by delaying cancer therapy. Young women are often diagnosed with aggressive cancers that need immediate treatment. Each pregnancy is precious, and especially in this population, the pregnancy may be the only option for completing a desire to have children. In 2010, the first epidemiologic data on cancer during pregnancy were published, based on the registry of the International Network on Cancer, Infertility and Pregnancy (INCIP). Two prospective follow-up studies of children that were antenatally exposed to chemotherapy were published.[1,2] The results are rather reassuring, indicating no clinical differences in neurocognitive and cardiac development between the treatment group and the control group. However, cancer treatment during pregnancy requires a strict obstetrical follow-up as it may be associated with an increased risk of spontaneous preterm labour and small-for-gestational age. The diagnosis and management of cancer during pregnancy create multiple medical, ethical and psychological challenges. A multidisciplinary approach is required when a pregnant patient is diagnosed with a malignancy. This study presents an overview on the incidence of cancer during pregnancy as well

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Conflict of interest: The authors have nothing to disclose and indicate no potential conflict of interest.

Keywords: cancer, diagnosis, neonatal outcome, oncological treatment, pregnancy, prognosis.

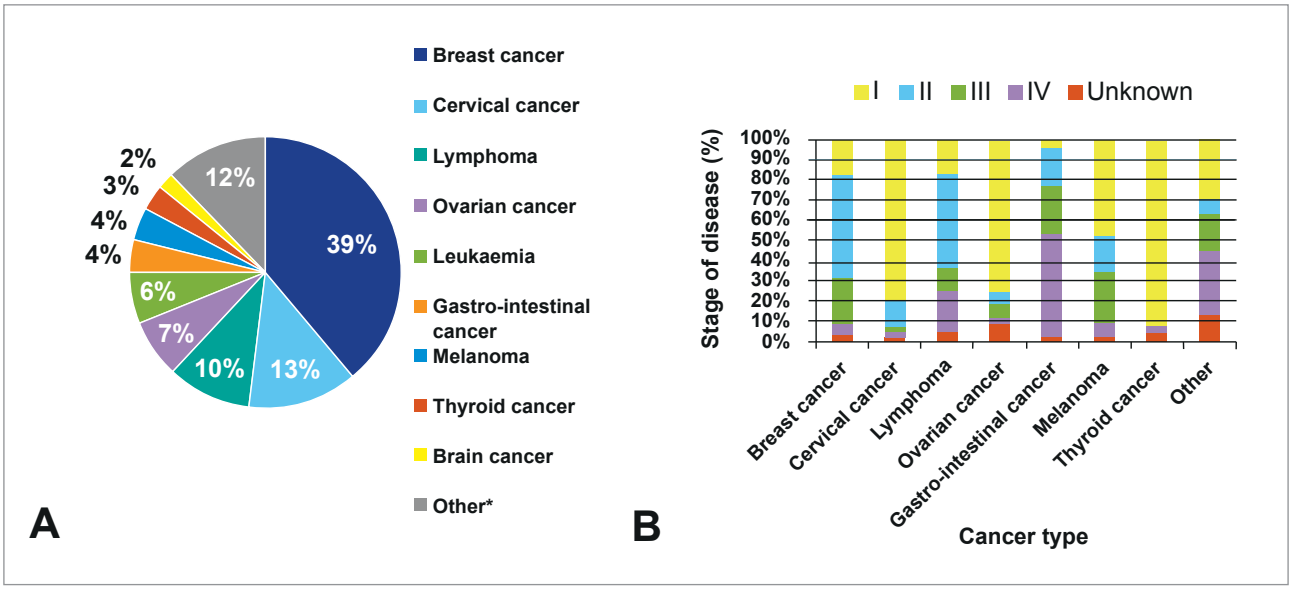

FIGURE 1. The distribution of different cancer types during pregnancy (A) and disease stage at diagnosis by cancer type (B). Disease stage was available for all solid cancers with tumour-node-metastasis (TNM) and International Federation of Gynecology and Obstetrics (FIGO) classification. Ovarian cancers include borderline ovarian tumours. *Consists of 25 different cancer types. Source: Interim-analysis on 1,170 patients, INCIP registry.[5]

as the diagnostic and therapeutic challenges in clinical decision making when cancer is diagnosed. It also focusses on current evidence of obstetrical, neonatal and paediatric outcome when cancer treatment is initiated during pregnancy.

INCIDENCE OF CANCER DURING PREGNANCY

In countries with decent epidemiological data, the incidence of cancer diagnosis during pregnancy is estimated to be 1 in 1000 pregnancies.[3] The increased awareness on cancer during pregnancy results in an increasing number of cohort studies on this subject. In 2005, the INCIP started registering patients diagnosed with cancer during pregnancy. The first update on the obstetrical and neonatal outcome of 215 patients was published in 2010.[4] An interim-analysis on 1170 patients, the largest cohort study published to date, was performed in 2017.[5] The most common cancers diagnosed during pregnancy were breast cancer (39%), cervical cancer (13%), lymphoma (10%) and ovarian cancer (7%). These are the cancers that are most diagnosed in women of reproductive age. Almost half of the patients (45%) was diagnosed in the second trimester of pregnancy. Distribution of malignancies and disease stage per malignancy are shown in *Figure 1.*

DIAGNOSIS AND STAGING

Cancer diagnosis is often delayed during pregnancy because physiological changes during pregnancy may mimic cancer symptoms. A systematic physical examination and a low threshold for further investigations is crucial for an early diagnosis. Radiation-free imaging is preferred in the staging of cancer during pregnancy. However, the most optimal imaging is required to decide on further management in treatment and follow-up of the patient. When deciding on radiographic imaging in pregnancy, one should consider that only the exams that will influence the management should be performed and that the foetal radiation exposure may not exceed 100 mGy, preferably 50 mGy. Whole-body diffusion weighted MRI is validated for the staging of cancer during all trimesters of pregnancy and is the preferred method.[6] Ultrasound can be performed safely during pregnancy. In breast cancer, a mammography (restricted to one mediolateral oblique record of both breasts and with abdominal protection in the second half of the pregnancy) is advised. Also, the sentinel-node procedure is considered to be safe enough during pregnancy, as long as the injected dose of technetium-99m labelled colloid is as low as possible.[6] The estimated average foetal radiation dose is 0.45 mGy. Blue dye, which is sometimes injected prior to surgery to facilitate the detection of the sentinel node, is not advised because this can potentially cause an anaphylactic reaction. The accumulation of radiation exposure of different radiological examinations needs sufficient attention. Contrast agents have to be used with caution in imaging. A breast MRI during pregnancy is not the preferred method, as gadolinium is contra-indicated. Foetal gadolinium exposure is associated with rheumatological, inflammatory or infiltrative skin conditions, stillbirth and neonatal death.[7]

Iodinated contrast may cause neonatal thyroid dysfunction. If it is used during pregnancy, the neonate's thyroid function has to be controlled within one week after birth. Tumour markers are never diagnostic, and the plasma concentration can be influenced by the physiological changes of pregnancy.[8] In the first trimester, the protein CA125 is commonly elevated (up to 35% of the normal value), whereas CA15.3 and SCC are more often elevated in the third trimester. Inhibin B, anti-Müllerian hormone (AMH) and lactate dehydrogenate (LDH) remain stable during pregnancy. Tumour markers of ovarian germ cell tumours (human chorionic gonadotropin [HCG], alpha-fetoprotein) cannot be assessed during pregnancy.

TREATMENT

According to current knowledge, based on animal studies and clinical experience, it is stated that oncological treatment can be initiated during pregnancy. In the management of cancer during pregnancy, the key principle is that the same treatment as non-pregnant patients are following should be offered. However, from foetal perspective, some treatments are not advised or even contra-indicated during pregnancy. If a pregnant patient presents with a very aggressive or metastatic disease early in pregnancy, it makes sense to question whether the pregnancy can be conserved safely. Preferably, decision-making should be performed in a specialised centre by a multidisciplinary team, taking the patient's perspective into account.

SURGERY

A surgical intervention can be performed safely during the pregnancy, as long as some adjustments are made. Physiological changes in pregnancy seek a different anaesthetic approach compared with non-pregnant patients. The maternal hemodynamic condition should stay as stable as possible, as this may influence directly foetal well-being. A stable oxygenation and blood pressure are mandatory to maintain an optimal foetal condition. In pregnancy, the use of oxygen is raised and the functional residual capacity of oxygen reduced, resulting in a fast desaturation when apnoea occurs. Maternal hypotension as a result of deep anaesthesia, hypovolaemia and vena cava compression may cause uterine hypoperfusion. Therefore, left-lateral tilt position from 20 weeks gestational age onwards is advised. From a viable duration of pregnancy (usually 24 weeks of gestation, depending on local hospital policies), intraoperative foetal monitoring is advised whenever possible. Post-operative foetal monitoring and foetal ultrasound belong to standard care. Tocolytics are advised during the second and third trimester of the pregnancy if uterine manipulation during surgery is inevitable.[9]

A laparoscopic intervention during pregnancy can be performed until 26-28 weeks of gestational age, depending on the surgeon's expertise.[10] An open introduction by Hasson is the preferred method. The umbilical port should be located 3-4 cm above the uterine fundus, even if this location is supra-umbilical. CO_2 insufflation of 10-15 mmHg can be safely used, and the intervention's maximal duration is ideally 90 minutes.

Post-operative analgesia is important because pain may provoke preterm uterine contractions. Non-steroidal anti-inflammatory drugs are contra-indicated in pregnancy, especially in the third trimester because of the risk of preterm closure of the ductus arteriosus. In the post-operative/hospitalisation setting, prevention of thromboembolism with low-molecular-weight heparin is indicated because of the hypercoagulable state of pregnancy.[11]

CHEMOTHERAPY

Chemotherapy is contra-indicated in the first trimester because it can potentially disturb organogenesis and is associated with miscarriage, foetal death and congenital malformations.[12] Starting from the second trimester of pregnancy, the administration of cytotoxic drugs seems to be safe. The transplacental passage of cytotoxic agents, including paclitaxel, carboplatin, doxorubicin and epirubicin, was investigated in a mouse and a baboon model. The foetal plasma concentrations were (considerably) lower than maternal plasma concentrations (*Table 1*).[13-15] Currently, the administered dose during pregnancy is calculated from the actual body weight on the treatment day, as no studies to date justify a change in dosage. However, physiological changes during pregnancy change the pharmacokinetic characteristics of cytotoxic agents, starting at four weeks of amenorrhea. Van Hasselt *et al.* has shown that physiological changes in pregnancy lead to a decrease in peak plasma concentrations and active medication in plasma (area under the curve [AUC]), as well as a raised distribution volume and elimination.[16] Theoretically, this finding may suggest that a standard treatment dose of cytotoxic agents, which is based on the actual body weight, may be suboptimal. But so far, the prognosis of patients treated for cancer during pregnancy does not seem to be different compared to non-pregnant patients.[17] However, more studies on follow-up data and pharmacokinetics are indicated to explore this phenomenon. The placenta acts as a barrier for the transfer of most chemotherapeutic drugs. Carboplatin and cyclophosphamide have the greatest potential to pass the placenta. However, data are insufficient to select a preferred regimen during pregnancy, and the decision for the chemotherapy type should be taken based on tumour biology and prognostic factors. Also, the

TABLE 1. Published data on transplacental passage of cytotoxic agents with advice for neonatal investigations.[13-15]

Cytotoxic agent	% of transplacental passage	Advice for neonatal investigations
Carboplatin	± 60%	Postnatal auditory test
Cyclophosphamide (active metabolite)	± 20%	
Doxorubicin	<10%	Postnatal echocardiography
Epirubicin	<10%	Postnatal echocardiography
Taxanes	<2%	
Vinca alkaloids	± 20%	

overall efficacy should be maintained to avoid compromising maternal outcome. Regimens that can be used relatively safely in breast cancer during pregnancy are 5-fluorouracil (F)-doxorubicin (A) or epirubicin (E)-cyclophosphamide (C) and taxanes (T; q1w [every week] or q3w [every three weeks] paclitaxel/q3w docetaxel).[18] Given the potential foetal toxicity of methotrexate (M), CMF should not be used during pregnancy. In the treatment of gynaecological cancers, the use of cisplatin, if indicated, should be considered carefully, as it might be associated with moderate bilateral hearing loss and ventriculomegaly.[19] Carboplatin is a more safe alternative, as case reports from exposed neonates are more reassuring.[20] In the selection of cytotoxic treatment in pregnancy, both potential foetal risks and maternal outcome should be taken into account.

OTHER SYSTEMIC THERAPY

Over the years, targeted therapy has been more developed and is now used in several cancer types. Mostly, the effect of these drugs during pregnancy is not known, and the use of targeted therapy in pregnant patients is discouraged because of the limited experience. IgG molecules are actively transported into the placenta by receptor mediated endocytosis, from the second trimester onwards. The use of trastuzumab during pregnancy has been associated with oligohydramnios, hypoplastic lungs and foetal death by its ligation to HER2-receptors that are present in the renal epithelium of the foetus.[21] Targeted therapy should be administered with care during pregnancy. For example, the use of vemurafenib in the treatment of advanced melanoma is associated with progressive intra-uterine growth restriction (IUGR). Also, anti-hormonal treatment should be avoided during pregnancy. Tamoxifen is associated with intra-uterine foetal death and birth defects like Goldenhar syndrome (oculo-auriculo-vertebral dysplasia), ambiguous genitalia and Pierre Robin sequence (triad of small mandible, cleft palate and glossoptosis).[22]

RADIATION THERAPY

Comprehensively, foetal radiation exposure during radiation therapy is much higher compared to the exposure during diagnostic procedures. Pelvic irradiation, with direct effect on the foetus, should never intentionally be performed during pregnancy. For the upper body (e.g., breast, brain, etc.), the total foetal exposure should always be calculated by a physicist using a phantom model and should not exceed 0.1 Gy. As pregnancy becomes more advanced, the radiation exposure will increase because of the proximity of the foetus to the radiation field.[23] By proper shielding of the foetus, a 50-70% dose reduction can be achieved.[24] In utero irradiation at all gestational ages may increase the risk of cancer during childhood.[25] In clinical practice, usually, radiation after breast conserving therapy will be postponed until after delivery to avoid the potential effects on the foetus. A large population-based cohort study revealed that starting radiation therapy shortly after breast conserving surgery is not associated with a better long-term outcome, suggesting that delaying radiation therapy should not necessarily be feared.[26] Whether or not radiation therapy should be started in pregnancy is always a dilemma, and the potential risks and benefits should extensively be discussed with the pregnant patient and her partner.

SUPPORTIVE THERAPY

In general, supportive medication in pregnant women should only be given if clinically indicated. During pregnancy, anti-emetics like metoclopramide, cyclizine and meclozine can be safely used.[27] In case of insufficient effect, ondansetron (5-

HT antagonist), aprepitant (NK1 antagonist) and alizapride (dopamine antagonist) may be considered with care. Also, corticosteroids, growth factors (GCS-F) and erythropoietins are not adequately studied for their safety during pregnancy requiring surveillance of the foetus. The use of hydrocortisone and prednisolone is preferred over dexa/betamethasone as these are extensively metabolised in the placenta, and relatively little will be detected in the foetal compartment. Repeated administrations of 12 mg betamethasone are associated with attention problems and cerebral palsy.[28] Methylprednisolone or hydrocortisone are therefore advised both for the prevention of anaphylactic reaction or as an anti-emetic drug.

OBSTETRICAL AND NEONATAL OUTCOME

Observational studies do not reveal a higher incidence of congenital malformations in children whose mothers were diagnosed with cancer or received cancer treatment during pregnancy.[5] The administration of chemotherapy is associated with spontaneous preterm labour and small-for-gestational age (SGA).[4] In the most recent, large cohort study, 21% (*vs* 3-7% in general population) of the foetuses exposed to chemotherapy during pregnancy was SGA.[5] Risk factors for SGA were maternal age at diagnosis of cancer, cytotoxic drugs (mainly platinum-based chemotherapy and alkylating agents) during pregnancy and systemic oncological disease. Forty-one per cent of the neonates was admitted in a neonatal intensive care unit (NICU). This risk was related to the oncological treatment (chemotherapy) during pregnancy. Ten per cent of the patients treated with chemotherapy experienced a spontaneous onset of preterm labour (*vs* 7-8% in the general population). The authors concluded that an intense obstetrical follow-up in a specialised centre when oncological treatment is initiated during pregnancy is mandatory. Prior to chemotherapy exposure, foetal growth as well as foetal Doppler assessment and cervical length should be controlled. In this population, iatrogenic preterm delivery is not uncommon, as delivery will be mostly planned to optimise the timing of oncological treatment. However, prematurity is associated with neonatal mortality and morbidity on the short and long term and should be avoided if possible. Delivery after minimum 34 weeks of gestation and ideally after 37 weeks of gestation should be intended. A safety interval of two or three weeks, depending of the chemotherapy regimen, between the last administration of cytotoxic drugs and delivery is advised to avoid haematopoietic suppression in the neonate. A vaginal delivery should be aimed for, unless there is an obstetrical contra-indication or when cervical cancer is *in situ*. In gynaecological cancers, a caesarean section can be performed simultaneously with surgical treatment. Although rare, the placenta should be sent for histological examination to detect possible placental metastasis.

PAEDIATRIC OUTCOME

The potential effect of malignancy and cancer treatment on foetal health is a concern. Chemotherapy during the first trimester of pregnancy should be avoided because of the risk of congenital malformations. The effects of chemotherapy beyond the first trimester could potentially affect the brain and heart development. The frontal brain functions (attention, memory and executive functions) are most vulnerable to cytotoxic drugs in adults and children.[29] Anthracyclines, commonly used in the treatment of breast cancer and haematological malignancies, are potentially cardiotoxic. To record the short- and long-term effects of cytotoxic drugs, children that were prenatally exposed to cancer treatment are followed in an international, multicentre study, integrated in the INCIP. The children are assessed with a general physical examination, cognitive testing and an heart function evaluation at regular time intervals (at birth, eighteen months, three years and then every three years until the age of 18). The first results on 70 children with a median follow-up period of 22.3 months were reassuring, indicating that the general health and growth, central nervous system and cardiac and auditory function of children born to mothers treated with chemotherapy during pregnancy did not differ from the general population.[1] These results were confirmed in a large case-control study that compared the development of the exposed children with healthy matched controls with a follow-up period of 36 months.[2] The outcome of 129 children whose mothers received a diagnosis of cancer during pregnancy was compared with 129 non-exposed children that were matched with respect to gestational age at birth and age at testing. The incidence of preterm delivery in the prenatal-exposure group was 61.2%. Cognitive, cardiac and general development did not differ between both groups. However, the study concluded that prematurity was correlated with a worse cognitive outcome, and this effect was independent of the cancer treatment. This is an important conclusion because an iatrogenic preterm delivery is common in the management of pregnant patients to optimise the timing of their oncological treatment. More safety data are, however, needed to better assess the long-term outcome.

MATERNAL OUTCOME

Whether a pregnancy can potentially affect malignant disease and maternal prognosis is a subject of debate. Especially in potentially hormone-dependent cancers, such as breast cancer, ovarian cancer and malignant melanoma, the effect

KEY MESSAGES FOR CLINICAL PRACTICE

1. Cancer treatment during pregnancy is possible but should be discussed in a multidisciplinary expert team, taking the patient's perspective into account.
2. Chemotherapy during pregnancy can be initiated in the second or third trimester. Obstetrical follow-up of foetal growth and cervical length is indicated.
3. Prematurity is associated with an adverse cognitive outcome of the neonate, independent of cancer or cancer treatment during pregnancy.
4. The prognosis of a cancer diagnosis during pregnancy does not differ compared to non-pregnant patients. An immediate cancer treatment is usually indicated and pregnancy termination does not change the prognosis. However, more data are needed.

of the raised oestrogen level during pregnancy is feared. Besides hormonal changes, increased vascularisation and immunological suppression may also have adverse effects on tumour development. Indeed, in breast cancer patients, the gestational physiologic alterations result in a delay in diagnosis and advanced stage disease. Because of the rarity of cases, analyses on this topic are mostly retrospective without information on other prognostic factors, resulting in inconsistent results. Large population-based cohort studies showed no increase in cause-specific death in patients with a cancer diagnosis during pregnancy. Data on 42,511 women aged 16 to 49 years, obtained from the cancer registry and the Medical Birth Registry of Norway, revealed no difference in cause-specific survival for women diagnosed with cancer during pregnancy or lactation, for most cancer types.[30] However, a diagnosis of malignant melanoma during pregnancy slightly increases the risk. Breast and ovarian cancer during lactation did show an increased risk of death. A recent meta-analysis that focused on the maternal outcome for patients with breast cancer diagnosis during pregnancy and patients with a postnatal diagnosis of breast cancer revealed an increased risk of death in both groups.[31] In a multicentre cohort study, the outcome of 311 pregnant patients with a breast cancer diagnosis was compared with 865 patients with breast cancer that was not associated with a pregnancy. Median follow-up was 61 months. Disease-free survival and overall survival were similar in both groups, adjusting for prognostic factors as maternal age, tumour histology and tumour stage.[17] Large-scale and case-controlled studies are necessary to consolidate these findings. There are no data suggesting that pregnancy termination might alter maternal prognosis. However, if a cancer is diagnosed before twelve weeks of gestation, the decision to continue pregnancy might delay the initiation of treatment. As a result, the consequences of this treatment delay should be clearly discussed with the patient.

CONCLUSION

The association of cancer with pregnancy is rare, but the incidence is expected to increase as more women delay child birth because of socio-economic reasons. In general, during pregnancy, an oncological treatment similar to the therapy in non-pregnant patients should be aimed for. Delay in diagnosis and treatment should be prevented since the maternal prognosis is stage and therapy dependent. The treatment options should be discussed by a multidisciplinary team, including a perinatologist, because not all treatment options are compatible with a pregnancy. Surgery, radiation therapy and chemotherapy can be considered, according to tumour type and gestational age. Follow-up in an experienced hospital is indicated because oncological treatment during pregnancy may adversely affect foetal growth and the risk of admission in neonatal intensive care units. Iatrogenic prematurity should be avoided where possible because this affects the cognitive outcome of the neonate, independent of the cancer or cancer treatment during pregnancy. The prognosis of cancer during pregnancy seems to be comparable to non-pregnant patients, but more data are needed to confirm this.

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