VIA MEDICA

REVIEW ARTICLE

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Pregnancy and malignant diseases — principles of management

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Oncology in Clinical Practice
2021, Vol. 17, No. 4, 176–182
DOI: 10.5603/OCP.2021.0024

ISSN 2450–1654
e-ISSN 2450–6478

ABSTRACT

Pregnancy-associated malignant diseases introduce multiple dilemmas to the multidisciplinary boards, related to both the oncological treatment as well as to obstetrical management. The most frequent oncological diseases diagnosed during pregnancy are breast cancer, oncohematological conditions, uterine cervix cancer and skin cancers. There are different clinical scenarios: interruption of the pregnancy and further use of the most appropriate oncological strategy; it is also possible to postpone the oncological treatment for the postpartum period with a watch-and-wait strategy until the foetus is mature and the delivery is planned. The third scenario includes concurrent treatment of both conditions: use of chemotherapy, radiotherapy and surgery during an ongoing pregnancy. Choosing among these scenarios is considering many factors, including type and stage of the malignant tumour, pregnancy term, desire and informed decision of the pregnant woman to keep or interrupt the pregnancy. The current review is focused on the basic principles of the oncological modalities (surgery, chemotherapy and radiotherapy) during pregnancy as well as their influence over the pregnant woman and the foetus, over the obstetrical management and the timing and mode of delivery, delivery anaesthesia, lactation and breastfeeding from the point of view of the evidence-based medicine.

Key words: pregnancy, malignant diseases, radiotherapy, chemotherapy, surgery

Oncol Clin Pract 2021; 17, 4: 176–182

Introduction

Pregnancy and neoplasia are a rare combination and thus evidence-based data and recommendations are limited [1]. In such a situation, the care for the mother and the foetus, the obstetrical and the oncological management should run in parallel, which may be rather challenging. The diagnosis of "cancer during pregnancy" introduces not only medical but many other problems, including ethical, personal, religious or even legal issues. Every cancer, diagnosed during pregnancy, qualifies the pregnancy as high-risk and thus the woman should be taken care of in specialized centres with experience both in oncology and obstetrics [2, 3]. It is known that the pregnancy itself does not worsen the oncological prognosis, but both the mother and the foetus may be susceptible to potential side effects of the different oncological treatments. Potential obstetrical complications include but are not only limited to intrauterine retardation of the foetus, preterm delivery with the delivery of an immature or small for the gestational age foetus. [1–4]

Epidemiology

— The rate of cancer during pregnancy is reported between 17–25/100,000 pregnancies [1].
— The most frequent neoplasia are:

1. breast cancer,
2. oncohematological diseases (lymphomas, leukaemia),
3. uterine cervix cancer,
4. skin cancers (basocellular, melanoma) [1].

Obstetrical therapeutic options

Obstetrical management depends on many patient-, foetus- and cancer-related factors, but treatment decisions most frequently take into consideration:

— cancer type,
— cancer disease stage,
— gestational age of the foetus (correctly determined) with screening for malformations)
— (lack of) Desire to keep the pregnancy [1–4]

The obstetrical management may be divided into:

1. Interruption of the pregnancy before the time when the foetus would capable of life [< 24th gestational week (g.w.)]. This is a relevant strategy in aggressive rapidly progressive cancers with poor prognosis, especially if diagnosed in the early weeks or months of the pregnancy.
2. Delay of the oncological treatment until the second trimester of the pregnancy in case of diagnosis in the first trimester (except for some haematological malignancies).
3. Oncological treatment during pregnancy. The oncological treatment is multimodal and consists of different therapeutic strategies, including surgery, chemotherapy and/or radiotherapy. They may be delivered in a different sequence given both the term of the pregnancy and the type and stage of the oncological disease.
4. Delay of the oncological treatment until after delivery. All modalities of the complex anticancer treatment or only some of them could be postponed, depending on the stage of the oncological disease, the possibility to deliver the treatment during pregnancy and the age of the pregnancy. This is another potential clinical scenario, considered in cases of a diagnosis of cancer close to the expected date of delivery [1].

Factors, influencing the treatment decisions in cancer during pregnancy

The general pregnancy and cancer management principles are related to the following aspects:

1. **Cancer-related factors** — oncological characteristics as a stage of the disease, histological type and potential treatment options. These determine the indications for anticancer management as well as the use of one or more treatment modalities (surgery, chemo- or targeted therapy, radiotherapy, etc.). The most appropriate treatment sequence is also crucial and may be modified by other non-cancer related factors.
2. **Foetus-related factors —** the age of the foetus and the stage of development and the degree of maturation are crucial. It strongly influences anticancer treatment choices as potential neonatal issues may develop as a consequence of the anticancer treatment.
3. **Mother-related factors** — treatment decisions are the priority of the pregnant woman and her family. Besides the decision to keep or not the pregnancy or the possibility for further pregnancies, the health status of the mother is essential when planning the anticancer treatment. Potential obstetrical issues and mode of delivery (Caesarean section versus vaginal delivery) are also considered, aiming at the most precise as a possible prediction of the time of delivery. Obstetrical factors are roughly summarized as:
   - time of delivery and choice of mode of delivery (vaginal versus Caesarean section),
   - anaesthesia during delivery (general versus local),
   - histological examination of the placenta,
   - breastfeeding and lactation [1].

Anticancer treatment during pregnancy — general principles

The oncological treatment is complex and consists most frequently of a multimodal approach. Systemic chemotherapy, radiotherapy or surgery may be used in sequence or different combinations and sequences.

Principles of surgery during pregnancy

General statements

Surgery is safe for the foetus after the first trimester. If the condition of the pregnant woman and the stage of the oncological disease permit, it is recommended to delay surgery until after delivery; it could also be done during delivery with an elective Caesarean section. Regional anaesthesia techniques are given preference over general anaesthesia [5].

Physiological changes, related to pregnancy and modifying the surgical process

Some physiological changes in the body of the mother are typical for the pregnancy period and may be relevant in the case of cancer during pregnancy. Between

the 6th and 34th g.w. the extracellular liquid increases with 3–4 litres due to the antidiuretic hormone (ADH) and the renin-angiotensin-aldosterone system (RAAS). This leads to haemodilution, a drop in the haemoglobin, haematocrit and albumin levels and the pharmacokinetics is therefore changed [6]. Additionally, the enlargement of the uterus and the increase of the pressure over the abdominal organs may lead to the development of gastroesophageal reflux with subsequent risk of aspiration syndrome, most frequently during the third trimester. Moreover, the pregnancy increases the thrombogenic risk as the coagulation factors VII, VIII, IX, X, XII and the plasminogen are in increased levels. The thromboembolic risk may be additionally increased due to venous stasis in the lower extremities or the neoplastic process itself. The postoperative immobilization with the damage of the vascular endothelium leads to the liberation of inflammatory mediators and may also increase the thrombogenic risk [1, 5].

Recommendations for surgery during pregnancy

— Recommendations for preoperative care
Conditions as diabetes, hypertension and medication intake should also be considered, compensated, controlled and if needed — corrected. The ultrasound examination with a record of the foetal heart sounds under obstetrical monitoring are safe, providing information for the foetal development and the actual status of the foetus. Corticosteroids (CS) may be prescribed in cases of risk for preterm delivery [5].

— Recommendations for intraoperative care
Interventions between 3rd and 5th g.w. should be avoided if possible due to a risk of defects in the neural tube. In case of surgery, the pregnant woman should be positioned in the left lying position after the 20th gestational week (not to compress the v. cava and to overload the heart). The risk of aspiration increases in the position of Trendelenburg (especially during laparoscopic procedures). Hemodynamic stability should be observed — hypotonia should be avoided, which could lead to a drop in the uteroplacental blood transfer, especially in foetal distress. The abdominal surgery could be planned for the second trimester when the risk of abortion is low, and the size of the uterus permits an adequate approach to the abdomen. A laparoscopic approach is not routinely recommended later than 26–28 g.w. The risks in laparoscopy are the development of hypercapnia, decreased blood flow due to the pneumoperitoneum and aspiration syndrome. The recommendations for the laparoscopic procedure, in case it should be done, include its performance by an experienced surgeon with a duration of the procedure less than 90 minutes, intraabdominal pressure 10–13 mm Hg; open approach for the first trocar, monitoring of the foetal heart sounds via cardiotocography and avoidance of intraprocedural hypotension [5, 7, 8].

— Recommendations for postoperative care
In postoperative care, an assessment of the foetal condition via ultrasound and obstetrical monitoring should be carefully performed. The pain control should be done via paracetamol, tramadol or NSAIDs. The use of these drugs during the 3rd trimester should be avoided as in 50–80% they may induce a preterm closure of the arteriosus duct with subsequent pulmonary hypertension. Prophylactic use of low-molecular heparin is mandatory in the postoperative period [9–11].
The risks in surgery during pregnancy are in general related to potential postoperative infections, that may induce preterm rupture of the foetal sac, which may subsequently induce foetal death, respiratory distress syndrome, need of mechanical ventilation, intraventricular haemorrhages or necrotic enterocolitis. In risk of preterm delivery, tocolytics are recommended to delay the delivery for 48 hours with the use of corticosteroids for stimulation of the foetal lungs' maturation [1, 3].

Principles of chemotherapy during pregnancy

Table 1 summarizes the main effects of chemotherapy on embryo and foetus development [12].

A. It cannot be done during the first trimester [1].
B. Chemotherapy, if used during the implantation period leads to the "all or nothing" phenomenon. It may cause malformations if used during days 10 to 56 of the pregnancy which the organogenesis period. This is the reason why chemotherapy treatment should not be used before 14th g.w. It should not be used after the 35th g.w. because chemotherapy can lead to neutropenia which increases the risk for infection of the mother and the baby [13, 14].
C. The risks for the foetus are intrauterine foetal retardation, preterm delivery, immaturity, neonatal toxicity — suppression of the bone marrow. This is the reason to recommend a minimum 3-weeks interval between chemotherapy and the expected time of delivery [15–18]. It is thus not routinely recommended to give chemotherapy after the 35th g.w.
D. The risk for the pregnant woman is of potential haematopoiesis suppression with further infections, bleeding or anaemia risks [19, 20].
E. Long-term (delayed) consequences over the foetus due to exposure to chemotherapy during their intrauterine foetal life. This is the reason to forbid the use of some target or cytotoxic agents (e.g., trastuzumab, bevacizumab, platinum salts, methotrexate, etc.).

Table 1. The main effects of chemotherapy during pregnancy on embryo and foetus development [12]

Period of pregnancy	Impact on embryo or fetus	Impact on the perinatal period	Long-term impact
First 4 weeks	Either pregnancy loss or no adverse effect	Not known	Not known
From 4 weeks to the end of 1st trimester	Malformations in 7–17% of children born to mothers receiving a single drug or 25% in case of combination therapy	Not known	Not known
Second or 3rd trimester	Case reports of reversible fetal heart toxicity for treatment with anthracyclines, particulary when trastuzumab is associated in the regiment	Preterm delivery and low birth weight (11%)	In general neuropsychological development is not affected. When retard is demonstarated, it is ascribed to prematurity
	Malformations are as frequent as in children barn to healty mothers	Myelosuppression (1–43% according to time of therapy suspension)	Older children frequently have internalzing behavioral problems Progressive left ventricular dysfunction several years afteranthracycline exposure

Endocrine therapy is contraindicated during pregnancy especially in breast cancer because is teratogenic and has been associated with birth defects in children of women who inadvertently have utilized the treatment during pregnancy [21, 22].

The incorporation of immunotherapy into clinical practice during pregnancy is recent and there is no sufficient data to speculate about their security in humans. For the time being, the utilization of these drugs during pregnancy is not recommended [23]. In animal models, anti-PD-1/PD-L1 and anti-CTLA-4 inhibitors during pregnancy are associated with an increase in abortion rates, stillbirths, premature delivery and higher incidence of infant mortality, especially when utilized during the third trimester [24–27].

Molecularly targeted agents are increasingly being used in modern oncology practice.[23] Most of these drugs are considered new in the practice and have no collected data of their effects while using during pregnancy. Imatinib increases the risk of spontaneous abortion and major malformations — exencephaly, encephalopathies and abnormalities in the skull bones. [23]. Trastuzumab is associated with oligohydramnios. Bevacizumab causes hypertension and proteinuria and it is assumed hypothesized that it might induce pre-eclampsia. Rituximab can cause immunosuppression by B-cell depletion in neonates [28].

— Neurocognitive development and results at school. There are several trials on this topic. A trial of Hahn (2006) on 40 children of age 2 months to 13 years reports one case of Dawn syndrome and 1 case of syndrome of deficit of attention [29]. In 70 children of age 1,5 to 17,6 years, Amant (2012) reports 2 cases with development of mental retardation but they are considered to be due to foetal immaturity [30]. The same author in 2015 reports poor cognitive results in 96 children of age 1.5–3 years that is also related to their prematurity in comparison non-exposed to the chemotherapy control group [31]. A study by Cardonick (2012) does not find a significant difference in cognitive development in 35 children of age 1,5 to 10,4 years in comparison with healthy controls [32].
— Behavioural changes (depression, anxiety, aggression or issues with the discipline). There are 2 studies with data on this topic: Amant (2012) reports 29% of such behavioural changes in 6 of 21 children of age 5–16 years. [29] Cardonick (2015) reports 23% cognitive issues (8 out of 35 children) in the exposed to chemotherapy group of children in comparison with 18 % (4 out of 22) in the control group [33].

Future trials are needed to study the long-term effects of chemotherapy on foetal fertility or the rates of secondary cancers.

Some non-antineoplastic medications which are widely used in oncology practice as supportive care also can be a cause of concern during pregnancy.

Bisphosphonates are generally contraindicated in pregnancy because they may reduce the calcium delivered to the foetus and induce skeletal malformations (reduced bone growth), low birth weight [34–36]. The granulocyte colony stimulation factors (GCS-F) can be used only in cases of severe neutropenia. In animal studies is observed that the use of GCS-F during the pregnancy can increase the spontaneous abortion rate and low birth weight with no increase in malformations. There is no such observation in human [37].

Table 2. Risks to the foetus of radiotherapy during pregnancy [39]

Gestational age (weeks)	Risks
Preimplantation (1)	Lethality
Organogenesis (2–7)	Lethality, gross malformations, growth retardation, sterility, cataracts, other neuropathology, malignant disease
Early foetal (8–15)	Lethality, gross malformations, growth retardation, mental retardation, sterility, cataracts, malignant disease
Mid foetal (16–25)	Gross malformations, growth retardation, mental retardation, sterility, cataracts, malignant disease
Late foetal (> 25)	Growth retardation, sterility, cataracts, malignant disease

Principles of radiotherapy during pregnancy — general recommendations

A. Malignant diseases, treated with radiotherapy (RT) — treatment recommendations for use during pregnancy. In cases of breast cancer, RT could be delivered until 18–19 g.w. as there is enough distance of the irradiated area to the pregnant uterus. In cases of supradiaphragmatic lymphadenopathy, RT could also be delivered in e.g., lymphomas. In brain tumours or head and neck cancers RT could be delivered at any time during pregnancy whereas in the uterine cervix RT cannot be delivered as it induces foetal death [38].

B. The risks for the foetus during RT (foetal dose < 0.1 Gy) are: intrauterine retardation of the foetus (small for their gestational age, risk of cardiovascular or metabolic complications, malformities (3–8 g.w.), mental retardation (8–25 g.w) and secondary neoplasia — 0–38 g.w. (e.g., leukaemia or solid paediatric tumours) (Tab. 2) [1, 38].

The combination of pregnancy and oncologic diseases leads to some specific neonatal and obstetrical problems.

The neonatal problems are due to the immaturity and/or the preterm delivery, both iatrogenic or as a result of intrauterine chemotherapy exposure. These are respiratory distress syndrome, temperature instability, excessive body weight loss, sepsis, hypoglycaemia, jaundice, risk of neuro-behavioural problems (poor results at school, need of special additional education) [1, 2].

The obstetrical problems are related to time and mode of delivery, anaesthesia of delivery, histological assessment of the placenta, breastfeeding and lactation.

1. Time of delivery
   Efforts should be made not to permit delivery before 37th g.w. to avoid iatrogenic immaturity. If chemotherapy is delivered during pregnancy, its last cycle should be no later than 3 weeks of the expected date of delivery [4, 40–42] to allow foetal bone marrow recovery [6].
2. Delivery mode
   It is determined by obstetrical indications. Vaginal delivery is the first method of choice and should be given priority due to the decreased blood loss, the shorter hospital stay and the lower risk of infections. The rates of elective Caesarean section in pregnant women with cancer is reported to be about 35% in the literature. There are some contraindications for vaginal delivery that should be considered: metastatic bone disease, brain metastases, uterine cervix cancer (the Caesarean sections aims at avoiding the trauma of the lower uterine segment) and vulvar cancer [1, 3].
3. Anaesthesia during delivery
   The gold standard for anaesthesia during and after delivery are the regional techniques: spinal or spinal-epidural anaesthesia. Contraindications to the regional anaesthesia may be brain tumours or metastases, metastatic bone disease, haematological neoplasia (e.g., acute leukaemia) due to the risk of hematoma and infection, leucopoenia and/or thrombocytopenia (risk of hematoma and infections) [1, 7].
4. Histological assessment of the placenta
   The histological assessment of the placenta is indicated in the search of metastases and most frequently these are registered in melanoma, lymphoma as well as in leukaemia [43].
5. Breastfeeding and lactation
   Chemotherapy during pregnancy leads to a decrease or interruption of lactogenesis. On the other hand, lactation during breastfeeding is not recommended as the cytostatics may be eliminated with the milk [13, 14, 41, 42]. Breastfeeding is possible after breast surgery or RT to the breast [44].

Conclusion

The management in case of pregnancy-associated cancer has different treatment strategies: interruption of the pregnancy and starting the treatment, a delay of the treatment after delivery or starting the treatment during the pregnancy. The most frequent complications of the chemotherapy during pregnancy are related to preterm

delivery risk as well as the risks, arising from the metabolism of the cytostatics, which mandates if possible, prediction of the last chemotherapy cycle no later than 3 weeks before the expected date of delivery. Surgical treatment and chemotherapy should be avoided before the 14th g.w. RT could be delivered as long as there is sufficient distance of the irradiated field from the pregnant uterus. Laparoscopy could be considered before the 26th g.w., taking into consideration the increased risk of aspiration and hypercapnia. The hemodynamic should be closely monitored during surgery and hypotonia should be rigorously avoided. Low molecular heparins are recommended in the postoperative setting and the foetus should be monitored via ultrasound and recording of the foetal heart sounds. During delivery, for the anaesthesia, local techniques should be given preference, whereas in the postoperative period, anaesthesia is given with analgesics. The mode of delivery is preferably vaginal.

Conflict of interest

The authors declare no conflict of interest.

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