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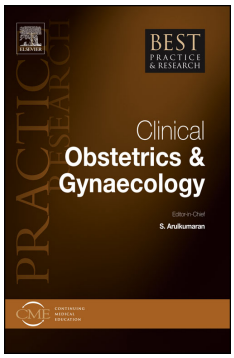

Management of Cancer in pregnancy

Frédéric Amant, MD PhD, Sileny N. Han, MD, Mina Mhallem Gziri, MD PhD, Tineke Vandenbroucke, Msc, Magali Verheecke, MD, Kristel Van Calsteren, MD PhD

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Frédéric Amant[1], MD PhD; Sileny N. Han[1], MD; Mina Mhallem Gziri[2], MD PhD; Tineke Vandenbroucke[1], Msc; Magali Verheecke[1], MD; Kristel Van Calsteren[3], MD PhD

1. Gynecologic Oncology, University Hospitals Leuven, and Division of Oncology, KU Leuven, Leuven, Belgium.
2. Obstetrics, Cliniques Universitaires St Luc, Brussels, Belgium.
3. Perinatalogy, University Hospitals Leuven, Belgium.

Correspondence to Frédéric Amant at Gynecologic Oncology, University Hospitals Leuven, and Division of Oncology, KU Leuven, Leuven, Belgium. Tel +32-16-344252, Fax +32-16-344205, frederic.amant@uzleuven.be

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ABSTRACT

A multidisciplinary discussion is necessary to tackle a complex and infrequent medical problem like cancer occurring during pregnancy. Pregnancy does not predispose to cancer but cancers occurring in women of reproductive age are encountered during pregnancy. Ultrasonography and magnetic resonance imaging are the preferred staging examinations, but also a sentinel node staging procedure is possible during pregnancy. Standard cancer treatment is aimed for. Operations can safely be done during pregnancy, but surgery of genital cancers can be challenging. The observation that chemotherapy administered during the second or third trimester of pregnancy, i.e. after the period of organogenesis, has little effect on the long term outcome of children adds to the therapeutic armamentarium during pregnancy. Cancer treatment during pregnancy adds in the continuation of the pregnancy and the prevention of prematurity.

KEY WORDS: pregnancy; cancer; radiotherapy; chemotherapy; surgery

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INTRODUCTION

The estimated incidence of cancer diagnosed during pregnancy is one per 1000 to 2000 pregnancies. Breast cancer, hematologic cancers, melanoma and cervical cancer are most frequently diagnosed, and correspond to the most common types of malignancy for women in this age group. Pregnancies complicated by a maternal cancer diagnosis are high risk pregnancies. The complex medical, ethical, psychological and religious issues arising in pregnant women with cancer demand care from a multidisciplinary team with obstetricians, oncologists, radiation oncologists, surgeons, pediatricians, geneticists, psychologists, teratologists and clinical pharmacologists. It is evident that curing the mother is the main priority. Correspondingly, the proposed treatment should adhere to standard treatment for non-pregnant patients. Recent studies have shown that oncologic treatment – with slight treatment modifications- is possible during an ongoing pregnancy, without jeopardizing fetal safety. Here, we aim to provide a concise update on current knowledge and recent research of cancer treatment during pregnancy.

DIAGNOSIS AND STAGING OF CANCER DURING PREGNANCY

Symptoms caused by a malignancy may mimic many common physiologic gestational symptoms such as nausea, fatigue, anaemia, vaginal bleeding/discharge, abdominal discomfort/pain or breast lumps. Ignoring or dismissing a warning sign can cause patient and also doctor's delay. All pregnant women deserve a careful clinical examination during check-ups, and special attention is necessary for persisting/worsening complaints.

Staging examinations for cancer during pregnancy should be as comprehensive as for non-pregnant women, but only be performed if they change clinical practice. The most important issue of radiologic examinations during pregnancy is fetal radiation exposure. A prestaging

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multidisciplinary discussion is proposed in order to reduce unnecessary radiographic examinations [1]. Ultrasonography and magnetic resonance imaging are preferred staging methods during pregnancy [2-4]. If radiographic exams are deemed necessary, total fetal radiation exposure should be 'as low as reasonably achievable' (ALARA), since radiation-induced effects are thought to be cumulative [5]. A threshold dose of 100 mGy for the 'deterministic' effects (e.g. lethality, malformations, mental retardation), which are dose-dependent, was determined by the American Association of Physicists in Medicine (AAPM) [4]. X-ray and computed tomography generate the highest dosages, but can often be performed safely with appropriate abdominal shielding. **Table 1** shows the fetal irradiation doses for these diagnostic tests, reproduced from AAPM [4].

In case of histopathologic examinations, gestational physiological hyperproliferative changes may influence tissue characteristics and thus the interpretation of tumour pathology. Therefore, the pathologist should be informed of the pregnant state [6]. Also, a tissue biopsy provides a more accurate diagnosis than fine needle aspiration cytology.

SURGERY DURING PREGNANCY

A vast experience of surgery during pregnancy for non-oncological reasons is available. Therefore, surgery is the least controversial type of oncologic treatment during pregnancy. Van Calsteren et al found that surgery was performed in 65.7% of women with any cancer treatment during pregnancy [7]. Surgery can be performed during all three trimesters. Anesthetic and surgical management during pregnancy require some modifications due to anatomic and physiologic changes and concerns about fetal safety. The basic objectives are **(a) optimal surgical outcome, (b) maternal safety, (c) fetal safety,** and **(d) prevention of miscarriage/preterm labour.**

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Optimal surgical outcome

Apart from genital cancer, the applied surgical technique is similar to non-pregnant cancer patients. Indications for breast conserving surgery and sentinel node biopsy are the same as in non-pregnant patients. The technique of abdominal surgery requires special attention, because of the presence of the expanding uterus, which dislocates other internal organs depending on gestational age. For advanced stage ovarian cancer, cytoreduction to no residual disease is not possible since the pouch of Douglas is virtually not accessible. Therefore, only a biopsy is taken during pregnancy, neoadjuvant chemotherapy is administered and cytoreductive surgery is postponed until after pregnancy. In case of cervical cancer, the pregnant uterus is involved and this is the most challenging situation. There is no standard treatment but several options exist according to the gestational age and stage of the disease. A detailed description of the rationale and indications for cervical cancer surgery is reported in a recent consensus statement [8]. Conization, simple trachelectomy (large conization) and pelvic lymph node resection can be done, especially until mid second trimester. Radical trachelectomy during pregnancy is a hazardous procedure and accompanied with significant blood loss. The obstetric outcome is rather poor since 6 out of 19 described cases (32%) resulted in early abortions related to the procedure [9] and therefore this procedure is not recommended during pregnancy.

There are no randomized controlled trials that compare laparoscopy and laparotomy during pregnancy. In case of laparotomy, a midline vertical incision is recommended for optimal exposure. In case of laparoscopy, open laparoscopy (Hasson technique) is recommended to avoid trocar or Verres needle injury to the uterus [10]. Port placement is important to avoid uterine perforation. The location of the first trocar should be at least 3 to 4 cm above the uterine fundus [11]. Instead of the umbilicus, an alternate position in the supraumbilical

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midline or Palmer's point (located 3cm from the midline and 3cm below the left rib cage) can be used. Depending on the procedure and experience of the surgeon, laparoscopy becomes technically difficult after 26-28 weeks gestational age due to the gravid uterus, and laparotomy is preferred [12]. There is an increased risk for fetal loss after laparoscopy for appendectomy (pooled relative risk of 1.91 [1.31-2.77]) [13], but it is unknown whether those results can be applied to a laparoscopic approach for oncologic surgery. Experts participating to a consensus meeting on gynaecologic malignancies during pregnancy recommend four prerequisites for laparoscopy during pregnancy: a maximal laparoscopic procedure time of 90 minutes, a pneumoperitoneum with a maximal intra-abdominal pressure of 10-13 mmHg, open introduction and an experienced surgeon [8].

Maternal safety

Physiologic changes that occur during pregnancy alter anesthetic management. Alveolar ventilation increases progressively to 70% at term. End-tidal PCO_2 falls to 33 mm Hg by the third month of pregnancy and functional residual capacity decreases up to 20% at term. Also, O_2 consumption increases significantly due to the O_2 requirements of the uterus, placenta and fetus [14]. Due to increased O_2 consumption and decreased functional residual capacity, apnea leads more rapidly to significant desaturation during pregnancy, therefore, thorough preoxygenation is critical. Requirements for volatile anesthetic agents decrease by about to 30%, beginning in the first trimester [15]. Dose adjustments of propofol are not necessary during pregnancy [16]. Preoperative medication as precaution to minimize risk of aspiration pneumonitis is often given, although the actual risk of aspiration appears to be small. The rate of gastric emptying is not delayed during pregnancy [17]. In a retrospective review of 51,086 first trimester and 11,039 second trimester pregnant patients undergoing deep sedation

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(without intubation) with propofol, no cases of perioperative pulmonary aspiration occurred [18].

Antibiotic prophylaxis depends on the specific procedure; cephalosporins, penicillins, erythromycin, and clindamycin can safely be administered during pregnancy.

Pregnancy, surgery, immobilization and malignancy are all risk factors for development of thrombo-embolic events. Therefore, prophylaxis with either unfractionated or low-molecular-weight heparin is advisable.

Fetal safety

Almost all commonly used anesthetics and premedicants are teratogenic in some animal studies. However, no anesthetic drug (premedicant, intravenous induction agent, inhalation agent, or local anesthetic) has been proven to be teratogenic in humans at any gestational age [19].

Fetal oxygenation is entirely dependent on maternal PaO_2, oxygen-carrying capacity (hemoglobin content), oxygen affinity, and uteroplacenta perfusion. Uterine blood flow will decrease in case of maternal hypotension (due to deep general anesthesia, hypovolemia, or vena cava compression). Vena cava compression can be avoided by a left lateral tilt position [20]. Maintaining normal maternal PaO_2, $PaCO_2$ and uterine blood flow is important, a stable maternal condition is the best guarantee for fetal well-being. One of the earliest signs of maternal distress is fetal distress, and the fetal condition can be critical by the time maternal hypotension manifests [20]. Continuous fetal heart rate monitoring during surgery is therefore advisable in case intervention (e.g. cesarean section) would be performed for fetal distress. This should be discussed preoperatively with the obstetrician and the parents, and mainly depends on gestational age, local policy and parent's consent. A fetal sleep pattern shows decreased variability and should be discerned from fetal distress. If the fetus is considered

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previable, it is generally sufficient to ascertain the fetal heart rate by Doppler or ultrasound before and after the procedure [21].

Prevention of miscarriage/preterm labour

Although data is limited, there is a consensus that tocolytic agents are indicated when manipulation of the pregnant uterus occurs [8]. Otherwise, routine prophylactic tocolytics are not indicated but should be considered perioperatively when signs of preterm labor are present, and in coordination with the obstetrician [22].

Postoperative analgesia

After surgery, adequate analgesia (paracetamol, non-steroidal anti-inflammatory drugs (NSAIDs), tramadol and morphine) and antiemetics (metoclopramide, meclizine, alizapride and ondansetron) can be prescribed [23,24]. The pharmacologic action of NSAIDs involves prostaglandine inhibition in the patient; transplacental transfer is noted, but their action in fetal tissue is unknown. Hernandez et al examined data from the National Birth Defects Prevention study (a multisite population-based, case-control study), and found that NSAIDs during early pregnancy, most commonly ibuprofen, aspirin and naproxen, were not associated with birth defects; although there were a few moderate associations with specific birth defects such as oral cleft, neural tube defect, anophthalmia/microphthalmia, pulmonary valve stenosis, amniotic bands/limb body wall defects, and transverse limb deficiencies [25]. NSAIDs administered in the third trimester of pregnancy may be associated with premature closure of the ductus arteriosus and possible pulmonary hypertension in the neonate in 50-80% of cases [26].

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RADIOTHERAPY DURING PREGNANCY

Whether a pregnant patient can be irradiated for cancer treatment without expected fetal harm should be discussed with a radiophysicist. In most cases where a pregnancy is still early and an adequate distance exists between the radiation field and the fetus, i.e. not exceeding the fetal irradiation dose of 100mGy, radiotherapy during pregnancy is expected to be safe. Exposure to ionizing radiation is associated with increased risk of biological effects to the fetus. Potential deterministic and stochastic effects have been reviewed in reports by the American Association of Physicists in Medicine (AAPM) and the International Commission on Radiological Protection (IRCP) [4,27]. They evaluated the results of animal studies, a series of human studies concerning the in-utero risk of cancer induction and effects on the developing brain, and also the recent advances in biological understanding of in-utero developmental processes were considered. The expected effects and risks are described in **table 2**[4,28,29]. Threshold doses for the 'deterministic' effects were determined by in vitro and in vivo research. Risks were clearly induced when a fetal dose of 100 mGy exceeded, uncertain between 50 and 100 mGy, and weak below 50 mGy. In contrast, no known threshold dose for the 'stochastic' effects are determined [30]. An estimation of the dose delivered to the fetus before treatment is necessary to assess the risk of radiation effects to the unborn child. There are 3 principal sources of dose outside the treated volume: (1) photon leakage through the treatment head of the machine, (2) radiation scattered from the collimators and beam modifiers, and (3) radiation scattered within the patient from the treatment beams [31]. In addition, when the energy of the treatment photons exceeds 10 megaelectron volt (MeV), a substantial neutron dose can be expected.

In the AAPM report, guidelines have been published on the estimation and reduction of the fetal dose. It is important to know the amount of photon leakage and the collimator scatter to the dose outside the field, because these components can be easily reduced by a factor of 2 to

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4 by placing a shield over the critical area **(Figure 1)**. However the design of proper shielding is difficult, because it involves the use of heavy materials, causing important considerations towards the methods of supporting and the number of times in which it must be (re)placed. Besides this, also the position and size of the fetus is important to know before planning of radiation therapy. Towards the end of pregnancy, the fetus lies closer to the field and could receive up to 10-15x the dose for the same treatment course [32,33]. To consider this, the treatment plan can be adapted by changing field angles, reducing the field size, modifying the beam energy, using a machine with multileaf collimator (MLC) and placing the patient so the lower collimator defines the field edge nearest the fetus [34]. It is important to calculate the fetal dose by measurements in a phantom before treatment is given. In a clinical setting the Monte Carlo methodology can be used to evaluate and estimate the fetal dose [35,36]. This computational procedure describes the calculation of the unshielded fetal absorbed dose for an average pregnant patient during 3-,6-, and 9-month gestational age. The models can be adopted for routine treatment planning, risk assessment, and the design of appropriate fetal shielding, in order to comply the ALARA principle.

Few data on long term follow-up of children exposed to radiation in utero are available [34,37-41]. Although numbers are small, the data are consistent and suggest that radiotherapy of upper body parts, before the third trimester and with shielding of the pregnancy, does not induce fetal harm.

CHEMOTHERAPY DURING PREGNANCY

The administration of chemotherapy is possible during the 2nd and 3rd trimester of pregnancy. Chemotherapy can be given from the 12-14th week of pregnancy until a gestational age of 35-37 weeks. Chemotherapy is relatively safe because of two reasons.

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Firstly, chemotherapy is administered after the first trimester, which is the period of organogenesis. Chemotherapy is associated with an all or nothing phenomenon during the implantation and induces malformations between the second and eighth week of pregnancy. This risk of malformation is estimated at 10 to 20%. Some organs are more vulnerable including the eyes, the ears, the hematopoietic system end the cerebral nervous system [42-44]. Aviles described 54 patients treated by chemotherapy during the first trimester of pregnancy without increase of malformations and explained this observation by a different renal, hepatic function and metabolism during the first trimester [45]. However, the timing of chemotherapy administration was poorly documented [46]. Therefore, chemotherapy is advised only after the 12-14th week of pregnancy because of teratogenicity risks [46,47].

Secondly, the placenta is a barrier and protects the fetus. For all investigated drugs, lower fetal concentrations were encountered. The transfer of chemotherapy is analyzed in animal models and in vitro [48-53] and depends on maternal pharmacokinetics, placental blood flow and the physicochemical drug properties [54]. The placenta is an active organ where placental transporters guide transplacental passage of drugs. This passage can be low (paclitaxel, 0-1%), intermediate (anthracyclines, 5-7%) or high (carboplatin, 60%) [50,51]. Although most cytotoxic drugs can be used during pregnancy, trastuzumab (Herceptin°) crosses the placenta, binds the Her-2 receptors of kidney epithelium, resulting in reduced amniotic fluid, lung hypoplasia and fetal death [55]. Currently no guidelines exist regarding chemotherapy dosages during pregnancy and the same dosages are used for non-pregnant and pregnant patients. If corticosteroids are administered as co-medication, methylprednisolone is preferred over dexa/betamethasone since placental metabolization results is less transplacental transfer [56].

The knowledge that chemotherapy can be used during pregnancy has three clinical implications. Firstly, the need for chemotherapy is not a reason to terminate the pregnancy.

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Secondly, the potential to administer chemotherapy allows a timely maternal treatment without delay. Thirdly, the use of chemotherapy during pregnancy adds in the prevention of iatrogenic prematurity. Despite this, more children need to be followed longer in order to provide more solid safety data. The different treatment options during pregnancy are presented in **Table 3**.

OBSTETRICAL AND PERINATAL MANAGEMENT

A checklist for care of pregnant patients with breast cancer is presented in **Table 4** [1].

At diagnosis it is important to evaluate fetal growth and development to date by ultrasound, and exclude pre-existing malformations.

A regular fetal monitoring by ultrasound for growth and fetal wellbeing is required. Special attention is required for fetal growth, preterm contractions and potential fetal anemia or cardiotoxicity after (anthracycline-based) chemotherapy [7]**.** After cervical surgery, serial cervical length measurements to assess for cervical incompetence are advisable.

A term delivery should be aimed for since (also late-)prematurity is associated with a significant neonatal and long-term morbidity [57,58]. If chemotherapy treatment is ongoing, delivery should be planned at least 3 weeks after the last cycle given during pregnancy to avoid drug accumulation in the neonate, and to avoid problems associated with hematopoietic suppression during delivery. For the same reason, chemotherapy should not be administered after 35-37 weeks since spontaneous labour becomes more likely.

The mode of delivery is mainly determined based on obstetrical indications. Similar to the general population, there are several important advantages to opt for a vaginal birth in most of these patients including reduced blood loss, reduced operative risk, reduced infection risk,

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shorter duration of hospitalization and better preservation of reproductive future. This is especially important for patients with myelosuppression after cancer therapy.

In some rare cases, like cancer metastasis to the long bones increasing the risk for fractures during labour precipitated by lithotomy position during labour and expulsion, a caesarean section is to be preferred. Active pushing can also be contra-indicated in central nervous system metastasis causing increased intracranial pressure. Assisted vaginal delivery can then be safely offered in most cases.

Although cervical intraepithelial neoplasia is not an indication for operative delivery, vaginal birth in women with cervical cancer can lead to fatal recurrences in the episiotomy. Operative delivery avoiding surgical trauma of the lower uterine part in order to prevent wound metastasis is therefore recommended in cervical cancer patients. In patients operated for vulvar cancer during pregnancy, vulvar scarring and the risk for vulvar trauma can be an indication for caesarean section.

Although placental metastases are rare, the placenta should always be analysed histopathologically after delivery [59]. Documented reports of maternal malignancy metastases in the placenta are rare. Since the first description in 1866, less than eighty cases have been described. Proven maternal metastasis to the fetus is exceptional, with only 11 cases reported so far. Malignancies spreading to the products of conception are melanoma (32%), leukemia and lymphomas (15%), breast cancer (13%), lung cancer (11%), sarcoma (8%), gastric cancer (3%) and gynaecologic cancers (3%), reflecting malignancies with a high incidence in women of reproductive age [60-62]. The presence of placental metastasis should alert the clinician to monitor the infant for development of malignant disease.

Breastfeeding can be allowed if the patient is motivated. Only when chemotherapy is ongoing postpartum or was administered in the last weeks before the delivery, one can assume transfer

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through breast milk to the baby. Any transfer should be avoided, and also in case of doubt, the threshold to stop breast feeding should be low, since a safe alternative is available.

When continuation of chemotherapy is required postpartum, an interval of a few days after a vaginal delivery is advised, after an uncomplicated caesarean section an interval of one week is fair.

LONG TERM FOLLOW-UP OF CHILDREN

Many clinicians used to withhold chemotherapy during pregnancy due to the unknown long term effects in the offspring. Recent evidence suggests that children perform well when chemotherapy is administered after the period of embryogenesis, thus after the first trimester of pregnancy. Chemotherapy administered beyond the first trimester could potentially have a negative influence on brain development. Especially the frontal brain regions, which are important for attention, memory and executive functioning, are a cause of concern. Mennes et al. [63] showed that chemotherapy can cause subtle differences in frontal functioning in children with leukemia treated with chemotherapy only compared to a matched control group. There were no differences in sustained attention, response inhibition or response organization. However, when a larger amount of information had to be processed or when attention had to be directed to specific stimuli, the impairment was more striking. Difficulties in selective attention and information processing were shown in longer reaction times. Nonetheless, patients were as accurate as controls.

One of the first reports on the long term effects of chemotherapy originates from Mexico. Aviles and colleagues [64] reported on a follow-up of 84 children born to mothers with haematological malignancies who received chemotherapy during pregnancy. A median follow-up period of 18.7 years (range 6-29) was administered. In all children, no congenital, neurological or psychological abnormalities were found and learning and educational

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performance were normal. Although complete neurological and psychological evaluations were performed by a physician, no intelligence tests were applied and other data were obtained by gathering information from schools.

Hahn et al. [65] reported on the outcome of children exposed to chemotherapy in utero. Parents or guardians were mailed a survey to assess the child's health, development, and performance in school if the child was of school age. Of the 57 women treated with chemotherapy in utero, 40 responded. One child had Down syndrome, but all other children were thought to have normal development. Only two children had special educational needs, of which one had attention deficit disorder and the other is the child with Down syndrome. Although these data are reassuring, they raise a methodological concern by only assessing development by a parent-report questionnaire.

In 2005, our research group initiated an international, multicentre, prospective, long-term follow-up study of children exposed to chemotherapy and/or radiotherapy in utero. Recently, an interim analysis was published [41]. In this study neuropsychological and behavioural development of children in Belgium, the Netherlands and Czech Republic was assessed using a standardized age-appropriate test battery. Children were screened neonatally and further at 18 months, 5-6 years, 8-9 years, 11-12 years, 15-16 years and 18 years.

The analysis on 70 children [41], with a median follow-up period of 22.3 months, showed age-appropriate cognitive development. For most children, Bayley Mental Developmental Index score and Wechsler Full-Scale IQ score were within normal range. Nonetheless, in 39% of the group of children from 5 years on, a disharmonic intelligence profile (a discrepancy between Verbal IQ and Performance IQ) was found, Verbal IQ being generally higher than Performance IQ, as opposed to 15% in the general population [66]. Although this variation does not represent neuropsychological dysfunction, disharmonic IQ profiles have been associated with learning and behavioural problems [67].

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The interim analysis showed average neuropsychological development. The results for verbal and non-verbal memory were within normal range. Furthermore, scores on focused attention, sustained attention, attention flexibility, divided attention and response inhibition were within normal range for the 12 children for whom attention function was assessed.

The average scores on the Child Behaviour Checklist, filled in by the parents of 21 children with a median age of 8.7 years, were within normal range, suggesting overall normal behavioral development. However, 29% of these children had an increased score for internalizing, externalizing and total problems, as opposed to 15% in the general population [68].

This interim analysis showed reassuring outcome for the children. Nonetheless, the results have to be interpreted with caution, as the sample size and follow-up period are not yet large enough to draw major safety conclusions. Additionally, there were two confounding factors, namely prematurity and maternal stress. In this sample, the median gestational age at birth was 35.7 weeks. Children who scored below average on the cognitive developmental test were mainly from the preterm group. This is comparable to other studies on cognitive development in preterm children, mentioning some cognitive delay compared to full-term children [69,70]. Second, maternal stress is frequently present when suffering from cancer during pregnancy. Antenatal maternal anxiety has been related to decreased performance on a sustained attention task in adolescence [71] and to hypothalamic-pituitary-adrenal-axis dysregulation and self-reported depressive symptoms in female adolescents [72].

Another concern is the potential effect of anthracyclines on the fetal heart. Anthracyclines are commonly used as a treatment for breast and hematological cancers - the most common cancer types during pregnancy – and are known to be associated with both acute and chronic cardiotoxicity. Avilés, Nero and Nambo [73] reported on a follow-up study of 81 children exposed to cytotoxic drugs, including anthracyclines, in utero. Children were between 9.3 and

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29.5 years (mean 17.1). No evidence of cardiac disease was found and echocardiogram and fractional shortening were normal. However, cardiac dimensions, wall thickness or diastolic function were not examined in this study.

In our follow-up study on 70 children [41], electrocardiography and echocardiography were performed. No congenital cardiac abnormalities were found. All variables for systolic and diastolic function were within normal ranges. However, a significant difference was found in ejection fraction and fractional shortening between the study group and a control group matched for age and gender, but this is not considered to be clinically relevant since values were within the normal range. Cardiac dimensions, wall thickness and left ventricular mass index were all within normal ranges. Gziri et al. [74] further investigated on that sample whether early functional changes could be detected using tissue Doppler imaging and two-dimensional speckle tracking echocardiography. 62 children were compared to a control group matched for age and gender. Patients had minor changes in left ventricular wall thickness associated with a slightly lower but normal ejection fraction. There were no differences between study group and control group in myocardial function and strain imaging and values were within normal ranges. These data are reassuring that cardiotoxic chemotherapy does not seem to affect cardiac outcome in children exposed to chemotherapy in utero. Nevertheless, although general health, neurocognitive and heart function are reported as in the general population, longer follow-up is needed to confirm these findings and also to assess fertility and the occurrence of secondary cancers later on in life.

MATERNAL PROGNOSIS

Whether pregnancy negatively influences maternal prognosis, has been a topic of debate for decades. Theoretically, several physiological changes of pregnancy, such as immunosuppression, hypervascularization, and increased hormonal exposure have been

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postulated as contributing factors to worse prognosis. Especially estrogen-dependent cancers such as breast cancer and melanoma are a great concern. Moreover, higher stage at time of diagnosis (due to patient and doctor's delay) can be another cause of worse prognosis.

Most historical case series are too underpowered to detect differences in prognosis when compared to stage-matched non-pregnant patients. Reassuringly, two recent studies have shown similar prognosis. Stensheim et al [75] performed a population-based cohort study; when comparing 516 women with a cancer diagnosis during pregnancy to 42,511 non-pregnant women aged 16-49 years, the risk of cause-specific death was not increased. In the largest observational study of breast cancer during pregnancy to date with 447 pregnant breast cancer patients, chemotherapy during pregnancy was not associated with worse outcome [76], and prognosis was similar to the non-pregnant patient [77].

SUMMARY

A multidisciplinary discussion is necessary to tackle a complex and infrequent medical problem like cancer occurring during pregnancy. Pregnancy does not predispose to cancer but cancers occurring in women of reproductive age are encountered during pregnancy. Ultrasonography and magnetic resonance imaging are the preferred staging examinations, but also a sentinel node staging procedure is possible during pregnancy. The observation that chemotherapy has little effect on the long term outcome of children adds to the therapeutic armamentarium during pregnancy. Cancer treatment during pregnancy adds in the continuation of the pregnancy and the prevention of prematurity. Participation to an international registry (www.cancerinpregnancy.org) of the International Network on Cancer, Infertility and Pregnancy (INCIP) is the best means to collect more data that ultimately will improve the care for our pregnant cancer patients.

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Tables and figures

Figure 1. Abdominal shielding of a pregnant uterus during irradiation of the breast.

Table 1.Fetal irradiation dose for different diagnostic tests (reproduced from AAPM) [4]

Table 2. Risks of radiotherapy to fetus during pregnancy (reproduced from AAPM) [4]

Table 3. Different cancer treatment options during pregnancy

Table 4. Checklist for care of pregnant patients with breast cancer (modified from Amant et al) [1]

Practice points

- The treatment of cancer during pregnancy is complex and not frequent. Therefore, a multidisciplinary approach is mandatory.
- Termination of pregnancy does not improve the maternal prognosis for breast cancer.
- Surgery during pregnancy is possible in all trimesters of pregnancy.
- Chemotherapy can safely be administered from 12-14 weeks gestational age onwards.
- Radiotherapy of upper body parts is safe during the first and second trimester of pregnancy when the distance to a small uterus is large.
- Cancer treatment during pregnancy adds in the prevention of prematurity.

Research agenda

- The long term follow up of children after antenatal exposure to chemo and or radiotherapy with an emphasis on general health, neurocognitive function, cardiotoxicity (in case anthracyclines were used), fertility and secondary cancers.
- The maternal prognosis after cancer treatment during pregnancy for the different tumour types.
- The impact of dilution of chemotherapy during pregnancy on the maternal prognosis.

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- The oncological safety of the sentinel node procedure during breast cancer surgery during pregnancy.

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CONFLICT OF INTEREST STATEMENT

None to declare.

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TABLES

Table 1: Fetal irradiation dose for different diagnostic tests (reproduced from AAPM) [4]

Diagnostic test	Fetal irradiation dose (mGy)
RX Thorax	0,0006
RX Abdomen	1,5 - 2,6
CT Thorax	0,1 - 13
CT Abdomen	8-30
PET	1,1 – 2,43

X-ray (RX)
Computed Tomography (CT)
Positron Emission Tomography (PET)

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Table 2: Risks of radiotherapy to fetus during pregnancy (reproduced from AAPM) [4]

Gestational age (weeks)	Risk
Preimplantation (1)	lethality*
Organogenesis (2-7)	lethality, gross malformations*, growth retardation*, sterility, cataracts, other neuropathology, malignant disease
Early fetal (8-15)	lethality, gross malformations, growth retardation, mental retardation*, sterility, cataracts, malignant disease
Midfetal (16-25)	gross malformations, growth retardation, mental retardation, sterility, cataracts, malignant disease
Late fetal (>25)	growth retardation, , sterility, cataracts, malignant disease
*** : high incidence**	

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Table 3: Cancer treatment options according to trimester of pregnancy

	Surgery	**Chemotherapy**	**Radiotherapy ***
1st trimester	Possible	Contra-indicated	Possible with adequate shielding
2nd trimester	Possible, consider intraoperative fetal heart rate monitoring ≥ 24-26 weeks	Possible ≥ 12 - 14 weeks	Possible with adequate shielding
3rd trimester	Possible, consider intraoperative fetal heart rate monitoring	Possible, aim for 3 week interval between 3-weekly chemotherapy and delivery	Contra-indicated **

*** of upper parts of the body; fetal exposure needs to be calculated**

**** individualization is important and may be possible in selected cases if distance is large enough**

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Table 4: Checklist for care of pregnant patients (modified from Amant et al) [1]

At diagnosis

- Confirm fetal viability and define duration of pregnancy
- Exclude pre-existing fetal anomalies by ultrasonography before examinations or interventions

Obstetrical follow up during oncological treatment

- Consider intraoperative fetal monitoring from 24 to 26 weeks' gestation onwards, according to local policy
- Chemotherapy is possible during second or third trimester
    - check for fetal wellbeing and general development
    - check for preterm contractions
    - check for intrauterine growth restriction
    - no chemotherapy after 35-37 weeks' gestation
- Radiotherapy is possible during first or second trimester
    - check for fetal wellbeing and general development
    - check for preterm contractions
    - check for intrauterine growth restriction

Delivery

- Mode of delivery is determined by obstetric indications (except for cervical cancer)
- Timing of delivery
    - preferably after 35-37 weeks' gestation
    - at least 3 weeks after last cycle of chemotherapy (for 3-weekly schemes) for sufficient recovery of bone marrow depression
    - in case preterm delivery is inevitable, fetal lung maturity is essential

Postpartum

- Examine placenta for metastatic disease

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- Oncological treatment can be continued immediately after vaginal delivery, and a week after uncomplicated caesarean-section
- Breast feeding
    - if physiologically possible e.g. after radiotherapy
    - contraindicated during and after chemotherapy

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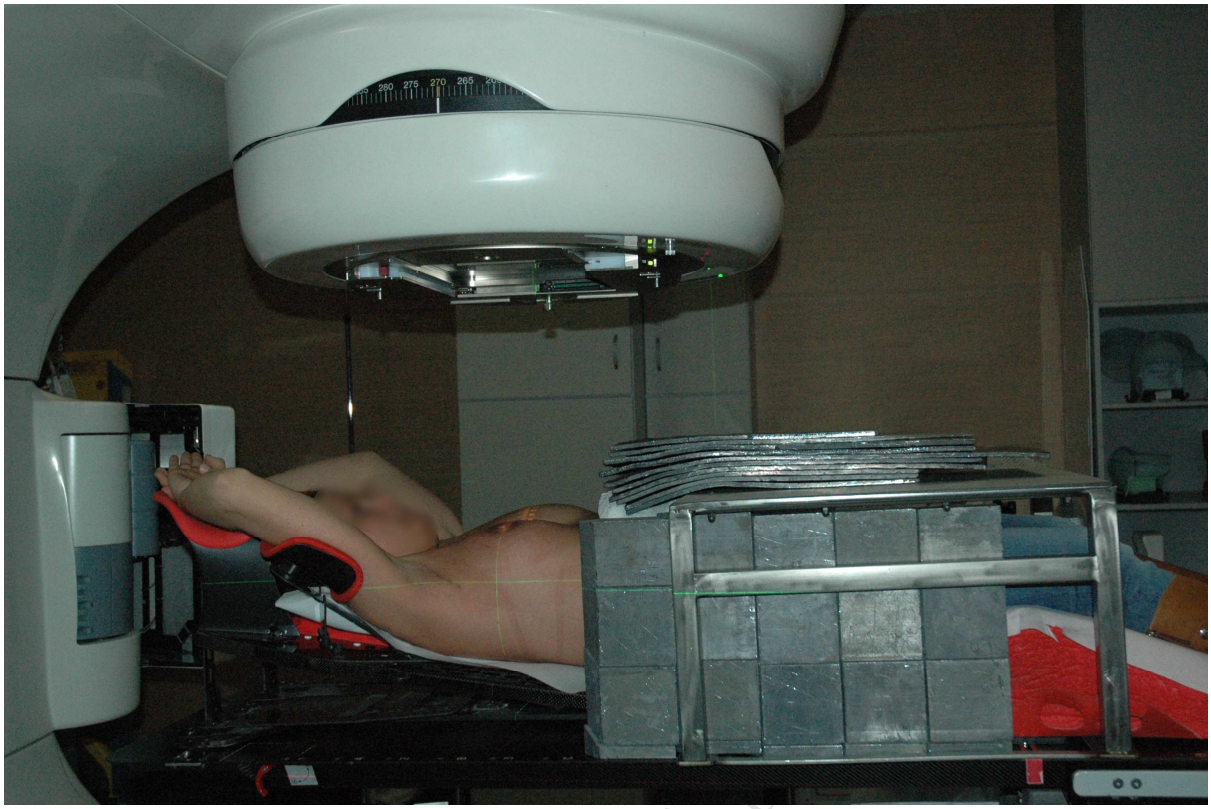

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