**Breast cancer in pregnancy**

*Frédéric Amant, Sibylle Loibl, Patrick Neven, Kristel Van Calsteren*

**Multidisciplinary Breast Cancer Center, Leuven Cancer Institute (LKI), Katholieke Universiteit Leuven, Belgium** (F Amant MD PhD, P Neven MD PhD); **German Breast Group, Departments of Medicine and Research, Klinikum Offenbach, Germany** (S Loibl MD PhD); **Obstetrics, University Hospital Gasthuisberg, Katholieke Universiteit Leuven, Belgium** (K Van Calsteren MD PhD)

*F. Amant is Sr. Clinical Investigator for the Research Fund-Flanders (FWO).*

Correspondence to: Professor Frédéric Amant,UZ Gasthuisberg Leuven, Herestraat 49, 3000 Leuven, Belgium. Tel: +32.16344252; Fax: +32.16344205. E-mail: [frederic.amant@uzleuven.be](mailto:frederic.amant@uzleuven.be)

**Abstract**

Breast cancer staging and treatment is possible during pregnancy. A staging and subsequent treatment strategy, should be defined in a multidisciplinary setting. Tumour biology, stage and gestational age at diagnosis determine the approach. Breast cancer surgery is possible during all trimesters of pregnancy. Radiotherapy is possible during pregnancy but the risk of poor fetal outcome is dependent on the fetal dose received and can be individually assessed. New insights add to the practice to administer chemotherapy from 14 weeks gestational age onwards. The state-of-the-art of breast cancer treatment applies to pregnant breast cancer patients, but tamoxifen and trastuzumab are contraindicated during pregnancy. Cancer treatment during pregnancy will decrease the need for early delivery and thus prematurity, a main concern in managing pregnant breast cancer patients. We summarize treatment options for management of breast cancer complicating pregnancy and address uncertainties and future research directions.

**Search strategy and selection criteria**

We searched Medline via Pubmed for meta-analyses, previous systematic reviews, retrospective case series and case reports published in English or German between 1980 and 2011 with the keywords “breast cancer”, “pregnancy”, “PABC”, “staging”, “sentinel”, “ionising’, “MRI”, “neonatal”, “chemotherapy”, “cytotoxic”, “biology”, “oestrogen receptor”, “progesterone receptor”, “HER-2”, “tumour biology”, “radiotherapy”, “surgery”, “long term” and “prognosis”. Reference lists were scanned to find any publication not already identified by our electronic search strategy.

**Introduction**

Although breast cancer was known in ancient times, it was uncommon until the 19th century, when improvements in sanitation and control of deadly infectious diseases resulted in dramatic increases in lifespan.1 One of the first reports on breast cancer during pregnancy dates from 1869.2 Pregnancy associated breast cancer (PABC) is defined as breast cancer diagnosed during pregnancy or within one year after delivery. In this Seminar, we address the co-incidence of invasive primary breast cancer and pregnancy (BCP). Cancer is the second leading cause of death in women during the reproductive years3 and breast cancer is the second most commonly diagnosed cancer in women under 35 in the United Kingdom.4 Breast cancer is one of the most diagnosed cancers during pregnancy but regional differences, the inclusion of postpartum breast cancers in some studies and the lack of information on the pregnant state in cancer registries add to a lack of reliable data based on a sufficient number of patients.5-7 As women in developed societies defer childbearing, and the incidence of most malignancies rises with increasing age, the condition where cancer complicates pregnancy is expected to become more common. Here, we discuss the diagnosis, treatment modalities and the impact on the foetus, obstetrical issues, and prognosis of breast cancer during pregnancy. Since randomized trials are virtually impossible, long term follow up registration studies only can address important uncertainties.

**Diagnosis of breast cancer during pregnancy**

***History and physical examination***

There are no specific risk factors for BCP. Genetic or environmental risk factors are similar to age-adjusted breast cancer in the general population. BRCA 1/2 mutation carriers might be at increased risk but the incidence of BCP is not higher.8 Given the young age, women should be referred to genetic counseling.

BCP typically presents as a painless lump palpated by the woman.9 Physiological breast changes, including engorgement, hypertrophy, and nipple discharge obscure detection for patient and physician. Therefore, delay in diagnosis is common, leading to more advanced stages at diagnosis. As a consequence and demonstrated in a large series, this results in more metastases and subsequent poorer outcomes.10

A clinically suspicious or persisting breast mass during pregnancy should be clarified and biopsied. Although approximately 80 % of breast lesions during pregnancy are benign11, ultrasound, mammography, and biopsy can be safely be used for ruling out breast cancer during pregnancy. A percutaneous biopsy of any lesion that does not meet all the criteria for a simple cyst is strongly recommended.12

***Diagnosis of breast cancer during pregnancy***

Diagnostic examinations of the breast during pregnancy require sufficient expertise since gestational changes alter the tissue structure. Breast ultrasonography is a first diagnostic tool during pregnancy when a breast mass and the axillary area need to be assessed, since it is non-ionizing and has a high sensitivity and specificity.13 Subsequently, when BCP is diagnosed, bilateral and multicentric disease can be ruled out with mammography.14,15 Magnetic resonance imaging (MRI) using contrast agents is possible during pregnancy though should only be used when it will alter clinical decision making, and when ultrasonography is inadequate.16 It needs to be emphasised that there are no well designed studies on the efficacy and safety of MRI studies during pregnancy. Also, studies have demonstrated that gadolinium-basedMRI contrastagents pass through the placental barrier and enterthe fetalcirculation. There is a potential for dissociation of the potentially toxic gadoliniumion from its chelate molecule and it is unclear what impact suchfree gadolinium ions might have if they were to be releasedin any quantity in the amniotic fluid.17 If MRI is needed, contrast agents that are preferentially used include Gadobenate dimeglumine (Multihance®) (approved by EMA and FDA) and Gadoterate meglumine (Dotarem®) (approved by EMA).18

***Pathological diagnosis of breast cancer in pregnant women***

Any suspicious breast lump or inflammatory breast (figure 1) needs further investigation. The standard examination to obtain a histological diagnosis is a *core biopsy* under local anaesthesia which can be performed safely during pregnancy with a sensitivity of around 90%.19 Milk fistulas after such a diagnostic procedure only rarely occur. However, gestational and puerperal hormones induce physiologic hyper proliferative changes of the breast. Diagnostic over interpretation is avoided when the pathologist is aware of the pregnant condition. Fine needle aspiration cytology carries the risk of false positive as well as false negative diagnosis due to the hyper proliferative cellularity of the mammary tissue and is not recommended during pregnancy.18

**Radiation in staging and treatment of BCP**

It is very well known that ionizing radiation interferes to a high degree with cell proliferation.20 Foetal exposure and damage may occur during staging examinations and radiotherapy and refers to the deterministic or stochastic effects of radiation. Deterministic effects may occur when foetal exposure exceeds the threshold dose of 0.1-0.2 Gy21 and include foetal death, malformations or impairment of foetal development. In contrast, there is no threshold dose for stochastic effects like a greater risk of childhood cancer and leukaemia. The 20% lifetime risk of contracting fatal cancer without radiation exposure contrasts with an added 0.06% risk at 0.01 Gy exposure.22 Therefore, the stochastic effects are considered limited though they should not be neglected as it was recently suggested.23 Radiological examinations are possible, though should only be applied when the results will change clinical management. When the estimated risk of metastatic disease is low, postponement of staging to after delivery can be considered. Radiologists and nuclear medicine physicians should be part of a diagnostic strategy planning to estimate the cumulative foetal toxicity and reduce the radiation exposure.18,24 Metastatic work up for breast cancer during pregnancy includes chest X-ray, liver ultrasound and a non contrast skeletal MRI. A radionuclear bone scan, with adequate hydration and an indwelling catheter to prevent retention of radioactivity in the bladder, can be used when MRI is not available or when additional information is needed.18 Positron emission tomography is not a standard staging tool in breast cancer and thus neither in BCP.

With respect to variations in foetal size, foetal radiation doses from therapeutic breast irradiation have been measured using anthropomorphic phantoms.25-27 It appears that apart from adequate shielding (50-75% dose reduction from leakage radiation and scatter21,28) fetal exposure can be reduced by increasing the distance from the field of irradiation. The absence of deterministic effects is confirmed by the birth of healthy children after radiotherapy during pregnancy.29-32 In the series of Luis et al, 13/109 offsprings had adverse outcomes, including perinatal deaths and neurologic deficits. It remains difficult to attribute these effects to radiotherapy since four of these had an exposure of less than 0.1Gy. Malformations occurred at all weeks of gestation.30 Follow up studies of atomic bomb survivors and their offspring (65 year follow up)36, of Chernobyl survivors (25 year follow up)33 and data obtained in low linear energy transfer ionizing radiation from medical exposure34, suggest a very low long term health risk after low dose exposure. Ionizing radiation can have serious health effects though the effects are known and quantifiable. The increased risk of poor fetal outcome after fetal radiation exposure is dependent on the fetal dose received.31 Individual risk assessment performed by a qualified medical physicist is necessary since the variations in radiation energy used, the stage of gestation and the individual treatment parameters such as field size, blocks, wedges, and shielding make any comparison impossible.26 Techniques to estimate and reduce fetal dose have been described.35 Results of such evaluation should be discussed with the woman and the family to allow her the opportunity to make an informed decision on the fate of her pregnancy.31

**Pathology**

The histopathologic and immunohistochemical findings of BCP are comparable to those in non-pregnant very young women (below 35 years).7,14,36-44 The majority of pregnant patients are diagnosed with infiltrating ductal adenocarcinomas (71-100%), and are often associated with aggressive behaviour, e.g higher incidence of grade 3 tumours (40-95%), lymphovascular invasion, and a high rate of oestrogen receptor negativity.15 Gestational breast cancer is associated with larger tumours and a higher incidence of nodal involvement (53-71%) when compared to tumours from non pregnant patients.37,39,40 Results on HER2 expression are inconclusive though data on more than 300 patients from our group demonstrated a HER2 positivity in 42%, which is the same (39%) as seen in non pregnant cancer patients <35 year.36,45 Based on pathological features, it appears that gestational breast cancer biology is not altered by the pregnancy though determined by age. The significance in preclinical models of a strong but transient increase of mammary stem cells during pregnancy that are highly responsive to steroid signaling despite the lack of hormone receptors remains to be studied.46

**Treatment**

Therapeutic strategies are defined by tumour biology, stage, gestational age and patient’s and her partner´s wishes. Counselling is crucial given the complexity and decisions should take into consideration the opinion of the patient. Also, a multidisciplinary team with all involved specialties should assess the medical (obstetrical, oncological, paediatric, and genetical), ethical, psychological and religious issues. The proposed treatment should adhere to the standard treatment for non-pregnant patients. Algorithms for the treatment of breast cancer for the three trimesters of pregnancy are depicted in figures 2-4. These algorithms refer to general principles and not necessarily all clinical situations are covered. These algorithms allow some adaptations to standard treatment when foetal health is a concern, e.g. some weeks delay to gain foetal maturity. There is no survival benefit for women who receive their treatment after delivery.36 Therefore, premature delivery or unnecessary delay in diagnosis or treatment in order to start treatment in the postpartum period should be avoided. Prematurity is a concern but can be prevented by cancer treatment during pregnancy.

***Pregnancy termination***

The maternal viewpoint on having children born, in utero and/or yet to be conceived, determines her choices and reactions when breast cancer is diagnosed and treated during pregnancy.47 Also, the decision to continue the pregnancy or not still remains a personal decision. The patient and her partner should be informed about the different treatment options and it should be made clear that termination of pregnancy does not appear to improve the maternal outcome.7 Data showing a worse trend for survival in BCP patients choosing for termination have not been matched for stage of disease.48,49 Probably, women with a worse prognosis at diagnosis, were encouraged to terminate their pregnancy.

***Surgery***

In general, surgery can be performed safely during any stage of pregnancy and most anaesthetic agents appear to be safe for the fetus.50,51,51,52 A multidisciplinary discussion among breast surgeons, anaesthesiologists and obstetricians should focus on the prevention of hypoxia, hypotension, hypoglycaemia, fever, pain, infections or thrombosis since these can have serious adverse effects on foetal development. Maternal care during the perioperative period is the best guarantee to ensure foetal well being. Foetal heart rate monitoring is used during surgery to detect foetal distress (figure 5) but its application should follow local guidelines. Preterm onset of labour can be provoked by pain for which sufficient painkilling is needed. Postoperative tocometry will identify any uterine activity that is masked by analgesia.18 Moreover, since pregnancy is an additional risk factor for thrombosis – apart from the malignant disease – thromboprophylaxis with low molecular weight heparin is indicated.

The choice of breast cancer surgery during pregnancy is made irrespective from the pregnant state and should follow the same guidelines as for non-pregnant women. Radiotherapy after breast conservative surgery is rarely a concern since most women receive chemotherapy with delay of radiotherapy until after delivery. Therefore, mastectomy is not mandatory and also breast conservative surgery can be done. In a recent series of 67 breast operations for BCP 53 few postoperative complications were observed. If breast reconstruction is considered, a prosthetic implant is possible. Considering physiologic alterations, autologous reconstructions should be delayed until after delivery.54

Sentinel lymph node staging can safely be used during pregnancy.21,55-57 The estimated absorbed doses at the level of epigastrium, umbilicus, and hypogastrium in non-pregnant patients after injecting 92.5 MBq of 99mTc sulphur colloid in the breast are below the 0.1-0.2 Gy foetal threshold absorbed dose, under the most adverse conditions.56,57 In another study, the dose to the abdomen was about 0.00045 Gy.58 In contrast, blue dye (Patent Blue®) carries a risk of an anaphylactic maternal reaction. During such a poor maternal condition, foetal distress is likely to be present. Therefore, the use of blue dye should be avoided during pregnancy.59 Although, sensitivity and specificity of sentinel lymph node biopsies during pregnancy have not been well established, technetium based identification is currently used successfully in pregnant women.55 A 1-day protocol requests lower radioactive dosages and is preferred.

***Cytotoxic treatment***

The effect of the administration of cytotoxic treatment on a pregnancy varies and depends on the gestational period during exposure. The fertilization/implantation period (first 10 days after conception) is characterized by an ‘all or nothing’ phenomenon. In this stage, the number of surviving omnipotent stem cells will determine whether a normal embryo will develop or a miscarriage will occur. Foetal damage in the period of the organogenesis (10 days - 8 weeks postconception) is more likely to result in congenital malformations. The 2nd and 3rd trimester of pregnancy are mainly characterized by foetal growth and maturation. Cytotoxic treatment in this period is not associated with foetal anomalies, albeit growth restriction, intra-uterine and neonatal death, prematurity, and haematopoietic suppression have been reported. Up till now, data on the long term outcome after prenatal exposure to cytotoxic treatment are scarce. Based on theoretical assumptions, neurodevelopmental problems, carcinogenesis, sterility, and genetic defects might have to be considered.21,60

*Chemotherapy for breast cancer*

Chemotherapy as part of primary breast cancer therapy is indicated in the majority of young breast cancer patients. In BCP the decision to administer chemotherapy should follow the same guidelines as in non-pregnant patients, taking into account the gestational age and the overall treatment plan (timing of surgery, need of radiotherapy, etc.). Chemotherapy can be adjuvant or neo-adjuvant and administered after the first trimester. Standard regimens such as 5fluorouracyl-epirubicin/doxorubicin-cyclophosphamide, epirubicin/doxorubicin-cyclophosphamide and taxanes (q1w-q3w paclitaxel/ q3w docetaxel) can be used. Although weekly epirubicin has been recommended based on foetal safety data61, its use cannot be recommended since it is not a standard treatment for breast cancer.62 We believe that clinicians should not put the maternal prognosis at risk to limit or reduce unproven fetal damage. The main advantage of weekly regimens during pregnancy refers to shorter nadir periods that may reduce complications when delivery unexpectedly occurs. Since there are alternatives and given the third space effect of methotrexate, cyclophosphamide-methotrexate-5fluorouracyl should not be used.18 Dose-dense regimens result in better disease free and overall survival, particularly in women with hormone receptor negative disease, which is common in patients with BCP.63 There are however very limited data on dose-dense, dose intensified chemotherapeutic regimens during pregnancy.

During pregnancy, changes in pharmacokinetics were documented for different drugs, including chemotherapy.64-66 Gestational alterations include an increased haemodynamic system, an increase in plasma volume and glomerular filtration rate, and hormonal changes in the hepatic function. For doxorubicin, epirubicin, paclitaxel and carboplatin, these changes have been shown to result in a decrease in plasma drug exposure (area under the curve) and peak plasma concentration (Cmax) and an increase in distribution volume and drug clearance.65,66 Hereby, questions arise on treatment efficacy of chemotherapy during pregnancy. There are arguments to state that inflammatory pregnancy-associated breast cancer has a similar chemo-sensitivity when compared to non-pregnant breast cancer patients, but we need to emphasize that this study only includes 11 patients with BCP.67 There is however no direct relationship between toxic tissue effects and prognosis. Although available outcome data on breast cancer during pregnancy are based on small numbers, they do not show a worse outcome when compared to non-pregnant women.5 Since there are currently no arguments to believe standard treatment in pregnant women would be less efficient, it is advised to prescribe the same drug regimens (based on body surface area or creatinine clearance) in pregnant and non-pregnant patients.15 The dosage should be calculated based on the actual weight and adapted to the weight changes during pregnancy.18

Since teratogenic effects of chemotherapy have been described, we can assume that at least a fraction of these drugs pass the placenta.60 Only a few case reports on transplacental transfer of chemotherapy in humans are available.68,69 However, the reported results from foetal blood sample collections after abortion or delivery within a few days after chemotherapy administration are not consistent, and therefore not conclusive. In a preclinical study on transplacental transfer of chemotherapy in a pregnant baboon model, varying passage rates were shown between different agents (table 1).70,71 When fetal and maternal plasma samples were collected simultaneously, for all tested chemotherapeutic drugs fetal concentrations were far below the maternal levels. Fetal doxorubicin, epirubicin, paclitaxel and docetaxel levels were below the level of quantification in 9, 3, 4 and 9 fetuses, respectively. Where measurable, fetal doxorubicin, epirubicin and paclitaxel were approximately 7.5, 4.0 and 1.4% respectively of the maternal levels at the same moment.70,71 These data confirm an important barrier function for the placenta but the difference between anthracyclines and taxanes is too small to define a preferable chemotherapy regimen in BCP patients. The placental filter function adds to fetal safety, especially when chemotherapy is administered after the first trimester. Anthracyclines and taxanes, have a high molecular weight, a high protein binding capacity, and are substrates of ATP-binding cassette transporters like p-glycoprotein, are confirmed to result in a low foetal exposure.64,72 Syncytiotrophoblast contains a variety of ABC-transporters, like p-glycoprotein and BCRP-1,73 for which several antineoplastic agents (vinca-alcaloids, anthracycline derivatives, taxanes and topotecan) are proven substrates. It has been shown that these drug transporters are able to reduce the drug concentrations at the foetal side to very low levels. On the other side, drugs which inhibit p-glycoprotein or which compete with cytotoxic drugs for the transporter might counteract this protection.74-76

For foetal protection, the administration of chemotherapy is considered contraindicated until a gestational age of 10 weeks. If a ‘safety period’ of 4 weeks is respected, chemotherapy may start from 14 weeks.77 In that scenario, the short term outcome, including the incidence of congenital malformations is well documented and reassuring for children that were prenatally exposed to chemotherapy for breast cancer.6,7,7,36,38,38,42,61,61,78,78-83 Different studies showed an increase in growth restricted foetuses when chemotherapy is applied during pregnancy.60 Yet, in studies looking specifically at breast cancer treatment in pregnancy, this increase was not seen.36,78 Although tumour types other than breast cancer and associated drug regimens seem to be at risk, numbers are too low to perform a subanalysis.6

Data on long term outcome after prenatal exposure to chemotherapy are scarce. A study that includes 84 children who were born to mothers who received chemotherapy during pregnancy for haematological malignancies and with a median follow-up of 19 years, did not show any congenital, neurological, immunological and psychological abnormalities including normal learning and educational behavior.84 However, the methodology of this study was poorly described. Based on a survey completed by 57 parents/guardians, a normal development was noted in most children at ages ranging from 2 to 157 months. Only 2 children required special attention in school: 1 had attention deficit disorder, whereas the other was a child with Down syndrome.38 In a small study, 10 children were between 2 months and 66 months of age when a full neurologic and cardiologic examination was performed. Whether the occurrence of a cortical malformation in a twin whose fraternal twin was normal, was related to cytotoxic drugs remains unclear. Otherwise, we encountered no development problems.80 The few studies that looked at the cardiac effect of chemotherapy in the foetus showed that acute myocardial dysfunction can appear during pregnancy with anthracyclines.60,69 However, follow-up with cardiac ultrasound in 81 children who received anthracycline treatment in utero ( age 9 - 29 years, mean 17 year) was reassuring.85

***Bisphosphonates for breast cancer***

Bisphosphonates could be demonstrated to be highly effective in premenopausal patients in combination with endocrine therapy.86 So far they have not been approved for the treatment of primary breast cancer. Animal studies with bisphosphonates have displayed maternal toxicity, foetal underdevelopment, embryolethality, hypocalcaemia and skeletal retardation during pregnancy. Bisphosphonates are therefore contra-indicated in pregnancy and have a FDA category C pregnancy risk. Their use in pre-menopausal women prior to conception or during pregnancy may pose a teratogenic risk because bisphosphonates remain in mineralised bone for several years. Reports on women treated before or during pregnancy with bisphosphonates, however, revealed no increased incidence of malformations or changes of the foetal bone modeling.87 If indicated in a pregnant patient with metastatic breast cancer hypocalcemia affecting the contractility of the uterus must be avoided.

***Hormonal agents in breast cancer treatment***

The use of hormonal agents such as selective oestrogen receptor modulators during pregnancy may disturb the hormonal environment, and should be delayed till after giving birth. Tamoxifen has the potential to induce foetal harm during pregnancy and is associated with birth defects including craniofacial malformations and ambiguous genitalia, and foetal death.88 Oral aromatase inhibitors are not indicated in premenopausal women.

***Targeted therapy for breast cancer***

Treatment with trastuzumab in HER2-positive tumours in pregnant women cannot currently be recommended. Fifteen fetuses were reported to be exposed to trastuzumab.89 Interference of trastuzumab with foetal renal epithelium in which HER-2 is strongly expressed90 may lead to oligohydramnios or anhydramnios, respiratory and renal failure (n=3) and eventually foetal death (n=4). Whereas a reduction in the volume of the amniotic fluid (oligo/anhydramnios) was noted in 8/15 pregnancies, the severity is linked to the duration of exposure. Although prolonged administration should be avoided18, trastuzumab for shorter periods appears less toxic. Also, in the surviving children renal function spontaneously recovered after withdrawal of the drug. Remarkable is the fact that while 11/15 patients were unintentionally exposed to trastuzumab in the first trimester of pregnancy, no congenital malformations were reported. This might be related to differences in transplacental transport of IgG-molecules, which gradually increases with the gestational age.91

New Drugs, like bevacizumab and tyrosine kinase inhibitors, enter the breast cancer scene. None of them were tested in patients with breast cancer during pregnancy, and therefore should not be used in pregnant patients.

***Supportive treatment in breast cancer***

Although it has not been properly documented, clinicians at least have the bedside experience that chemotherapy induced side effects are less pronounced in pregnant women. Based on a general principle during pregnancy, not to use any medication when not strictly indicated, supportive treatment should only be administered if indicated. Growth factors for white and red blood cells are used during pregnancy without adverse events reported, but the clinical evidence of their safety during pregnancy remains limited. If indicated according to current guidelines for growth factor support during chemotherapy, there are no arguments to withhold these agents.77,92 Special attention should be paid to the use of steroids. Methylprednisolone and hydrocortisone are extensively metabolized in the placenta and are therefore the preferred steroids to use during pregnancy77. Dexamethasone and betamethasone cross the placenta and the repeated administration of these steroids is associated with increased incidences of attention problem and higher rates of cerebral palsy and an increased incidence of cleft palate during the first trimester.93,94

**Prognosis**

Pregnant women are less likely to be diagnosed with stage I but 2.5-fold more likely diagnosed with advanced disease than non-pregnant women.95,96 Although several papers address the maternal prognosis, the studies always refer to PABC, thus including breast cancer diagnosis within 1 year after delivery. The fraction of breast cancers diagnosed during pregnancy is not analysed separately or to small to control for all prognostic factors. Only in a collaborative setting with knowledge of prognostic factors and follow up data, the maternal prognosis can be explored.

**Prenatal care**

Apart from the serious maternal illness, also the examinations and oncological treatment might interfere with normal foetal development. Therefore, these patients should be followed in a unit for high-risk obstetrics. In general these patients should be followed and treated as other high risk obstetric patients, e.g. with regard to lung maturation and mode of delivery.15,18 Although there are no guidelines for obstetricians to monitor pregnant patients treated for breast cancer, we present some considerations in table 2. Before staging examinations or oncological treatment is started, foetal structural development and growth should be evaluated to exclude pre-existing anomalies.15 Since in a series of 215 patients, preterm labour and growth restriction was increased,6 perinatologist should pay special attention to preterm labour and foetal growth restriction.6 When anthracyclines are used, special consideration should be taken into account when maternal conditions involving the cardiovascular system are apparent (for example pre-eclampsia). When delivery is scheduled, it is important to aim for a term delivery (> 37 weeks of gestation) since prematurity contributes to the cognitive and emotional development of children.97,98 When BCP is diagnosed in the third trimester and when only one cycle of chemotherapy is needed to reach fetal maturity, delivery at 35 weeks and start of chemotherapy postpartally can be considered. This is a balance between the risks of late prematurity and the poorly documented long term outcome after chemotherapy exposure late in pregnancy. It is necessary to respect a 3 week time-interval between the last cycle of chemotherapy and the delivery in order to avoid problems associated with hematopoietic suppression (bleeding, infection, anaemia) in the patient and neonate, and to avoid drug accumulation in the foetus.15,18,99 We advise to examine the placenta of all pregnant patients with cancer for metastatic disease. For breast cancer, fourteen cases of placental metastases have been described. Up till now there are no reports of foetal metastases of breast cancer.100 Postpartum oncological treatment, including chemotherapy and radiotherapy, can be restarted immediately after a vaginal delivery. After an uncomplicated caesarean section a time interval of one week is recommended before oncological treatment is continued. After chemotherapy during pregnancy primary inhibition of milk production is advised to prevent accumulation of lipophylic agents as taxanes in the milk. Breastfeeding in the first weeks after chemotherapy is, in the absence of safety data, not recommended.

**Conclusion**

Breast cancer treatment during pregnancy is possible and termination of pregnancy is not likely to improve the prognosis. Breast cancer during pregnancy is not an emergency and the time needed for consulting an expert team is not worsening the prognosis. A first multidisciplinary discussion refers to a diagnostic strategy aiming to reduce the burden of foetal radiation exposure. Non ionizing examinations are preferred and staging examinations that are likely to alter breast cancer treatment during pregnancy are performed. A second multidisciplinary discussion determines the therapeutic strategy that should adhere as closely as possible to standardized protocols for non-pregnant patients, but considers foetal safety issues. Future studies need to determine the impact of lower serum levels of chemotherapy due to the physiologic pregnancy associated alterations. Especially in these women, the maternal prognosis needs to be determined. Although current data suggest chemo- and radiotherapy can be used during pregnancy, a better documentation of the long term outcome of the children is needed. Prematurity will add to the long term outcomes and should be avoided. Randomisation of patients is impossible and international registries (www.cancerinpregnancy.org, [www.germanbreastgroup.de](http://www.germanbreastgroup.de)) only can accrue numbers that allow more robust conclusions. A task force within the European Society of Gynaecological Oncology is dedicated to this subject and welcomes active members.

**Conflict of interest statement**

There are no conflicts of interest. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

**Authors’ contributions**

FA designed the concept. All authors were involved in literature search, writing and final approval of the manuscript.

**Table and Figure legends**

**Table 1:** Results of transplacental transfer of chemotherapeutic agents in a pregnant baboon model, based on simultaneously collected maternal and foetal plasma samples70,71

**Table 2:** Check list when prenatal care in breast cancer patients is designed

**Figure 1:** Inflammatory breast cancer during pregnancy with enlarged axillary lymph nodes

**Figure 2:** Algorithm for the treatment of breast cancer diagnosed during the first trimester of pregnancy

**Figure 3:** Algorithm for the treatment of breast cancer diagnosed between 12-28 weeks of pregnancy

**Figure 4:** Algorithm for the treatment of breast cancer diagnosed from 29 weeks of pregnancy onwards

**Figure 5:** Left lateral tilt position and foetal heart rate monitoring during breast cancer surgery

Reference List

1. Aronowitz RA. Unnatural history: breast cancer and American Society.Cambridge, UK, Cambridge University Press, 2007, 22-24.

2. Klotz HAWE. Ueber mastitis carcinomatosa gravidarum et lactantium. *Diss Halle-Wittenberg* 1869.

3. Minino AM, Xu J, Kochanek KD, Tejada-Vera B. Death in the United States, 2007. *NCHS Data Brief* 2009; 1-8.

4. Cancer Statistics registration: Registrations of cancer diagnosed in 2007, England. Series MB1 no.38 ed. London, Office for National Statistics, 2010.

5. Stensheim H, Moller B, van Dijk T, Fossa SD. Cause-specific survival for women diagnosed with cancer during pregnancy or lactation: a registry-based cohort study. *J Clin Oncol* 2009;**27**: 45-51.

6. Van Calsteren K, Heyns L, De Smet F, et al. Cancer during pregnancy: an analysis of 215 patients emphasizing the obstetrical and the neonatal outcomes. *J Clin Oncol* 2010;**28**: 683-9.

7. Cardonick E, Dougherty R, Grana G, Gilmandyar D, Ghaffar S, Usmani A. Breast Cancer During Pregnancy: Maternal and Fetal Outcomes. *Cancer J* 2010;**16**: 76-82.

8. Wohlfahrt J, Olsen JH, Melby M. Breast cancer risk after childbirth in young women with family history (Denmark). *Cancer Causes Control* 2002;**13**: 169-74.

9. Molckovsky A, Madarnas Y. Breast cancer in pregnancy: a literature review. *Breast Cancer Res Treat* 2008;**108**: 333-8.

10. Ulery M, Carter L, McFarlin BL, Giurgescu C. Pregnancy-associated breast cancer: significance of early detection. *J Midwifery Womens Health* 2009;**54**: 357-63.

11. Collins JC, Liao S, Wile AG. Surgical management of breast masses in pregnant women. *J Reprod Med* 1995;**40**: 785-8.

12. Taylor D, Lazberger J, Ives A, Wylie E, Saunders C. Reducing delay in the diagnosis of pregnancy-associated breast cancer: how imaging can help us. *J Med Imaging Radiat Oncol* 2011;**55**: 33-42.

13. Navrozoglou I, Vrekoussis T, Kontostolis E, et al. Breast cancer during pregnancy: a mini-review. *Eur J Surg Oncol* 2008;**34**: 837-43.

14. Ishida T, Yokoe T, Kasumi F, et al. Clinicopathologic characteristics and prognosis of breast cancer patients associated with pregnancy and lactation: analysis of case-control study in Japan. *Jpn J Cancer Res* 1992;**83**: 1143-9.

15. Loibl S, von Minckwitz G, Gwyn K, et al. Breast carcinoma during pregnancy. International recommendations from an expert meeting. *Cancer* 2006;**106**: 237-46.

16. Oto A, Ernst R, Jesse MK, Chaljub G, Saade G. Magnetic resonance imaging of the chest, abdomen, and pelvis in the evaluation of pregnant patients with neoplasms. *Am J Perinatol* 2007;**24**: 243-50.

17. Kanal E, Barkovich AJ, Bell C, et al. ACR guidance document for safe MR practices: 2007. *AJR Am J Roentgenol* 2007;**188**: 1447-74.

18. Amant F, Deckers S, Van Calsteren K, et al. Breast cancer in pregnancy: recommendations of an international consensus meeting. *Eur J Cancer* 2010;**46**: 3158-68.

19. Shannon J, Douglas-Jones AG, Dallimore NS. Conversion to core biopsy in preoperative diagnosis of breast lesions: is it justified by results? *J Clin Pathol* 2001;**54**: 762-5.

20. Hall EJ. Scientific view of low-level radiation risks. *Radiographics* 1991;**11**: 509-18.

21. Kal HB, Struikmans H. Radiotherapy during pregnancy: fact and fiction. *Lancet Oncol* 2005;**6**: 328-33.

22. Doll R, Wakeford R. Risk of childhood cancer from fetal irradiation. *Br J Radiol* 1997;**70**: 130-9.

23. Rajaraman P, Simpson J, Neta G, et al. Early life exposure to diagnostic radiation and ultrasound scans and risk of childhood cancer: case-control study. *BMJ* 2011;**342**: d472.

24. Nuclear medicine resources manual.- Vienna : International Atomic Energy Agency, 2006.STI/PUB/1198 ISBN 92-0-107504-9. 2009.

25. Van der Giessen PH. Measurement of the peripheral dose for the tangential breast treatment technique with Co-60 gamma radiation and high energy X-rays. *Radiother Oncol* 1997;**42**: 257-64.

26. Antypas C, Sandilos P, Kouvaris J, et al. Fetal dose evaluation during breast cancer radiotherapy. *Int J Radiat Oncol Biol Phys* 1998;**40**: 995-9.

27. Mazonakis M, Varveris H, Damilakis J, Theoharopoulos N, Gourtsoyiannis N. Radiation dose to conceptus resulting from tangential breast irradiation. *Int J Radiat Oncol Biol Phys* 2003;**55**: 386-91.

28. Han B, Bednarz B, Xu XG. A study of the shielding used to reduce leakage and scattered radiation to the fetus in a pregnant patient treated with a 6-MV external X-ray beam. *Health Phys* 2009;**97**: 581-9.

29. Fenig E, Mishaeli M, Kalish Y, Lishner M. Pregnancy and radiation. *Cancer Treat Rev* 2001;**27**: 1-7.

30. Luis SA, Christie DR, Kaminski A, Kenny L, Peres MH. Pregnancy and radiotherapy: management options for minimising risk, case series and comprehensive literature review. *J Med Imaging Radiat Oncol* 2009;**53**: 559-68.

31. de Wildt SN, Taguchi N, Koren G. Unintended pregnancy during radiotherapy for cancer. *Nat Clin Pract Oncol* 2009;**6**: 175-8.

32. Munter MW, Wengenroth M, Fehrenbacher G, et al. Heavy ion radiotherapy during pregnancy. *Fertil Steril* 2010;**94**: 2329-7.

33. Health Effects Due to Radiation from the Chernobyl Accident. Annex D of UNSCEAR 2008: Sources and Effects of Ionizing Radiation. Volume 2: Effects. *J Radiol Prot* 2011;**31**: 275-7.

34. National Research Council. Beir VII: Health Risks from Exposure to Low Levels of Ionizing Radiation. Washington, USA: National Academies Press; 2002.

35. Stovall M, Blackwell CR, Cundiff J, et al. Fetal dose from radiotherapy with photon beams: report of AAPM Radiation Therapy Committee Task Group No. 36. *Med Phys* 1995;**22**: 63-82.

36. Loibl S, Amant F, Kaufmann M, et al. 313 patients with breast cancer during pregnancy - a prospective and retrospective registry (GBG-20 / BIG02-03). 2010.

37. Halaska MJ, Pentheroudakis G, Strnad P, et al. Presentation, management and outcome of 32 patients with pregnancy-associated breast cancer: a matched controlled study. *Breast J* 2009;**15**: 461-7.

38. Hahn KM, Johnson PH, Gordon N, et al. Treatment of pregnant breast cancer patients and outcomes of children exposed to chemotherapy in utero. *Cancer* 2006;**107**: 1219-26.

39. Middleton LP, Amin M, Gwyn K, Theriault R, Sahin A. Breast carcinoma in pregnant women: assessment of clinicopathologic and immunohistochemical features. *Cancer* 2003;**98**: 1055-60.

40. Reed W, Hannisdal E, Skovlund E, Thoresen S, Lilleng P, Nesland JM. Pregnancy and breast cancer: a population-based study. *Virchows Arch* 2003;**443**: 44-50.

41. Shousha S. Breast carcinoma presenting during or shortly after pregnancy and lactation. *Arch Pathol Lab Med* 2000;**124**: 1053-60.

42. Berry DL, Theriault RL, Holmes FA, et al. Management of breast cancer during pregnancy using a standardized protocol. *J Clin Oncol* 1999;**17**: 855-61.

43. Bonnier P, Romain S, Dilhuydy JM, et al. Influence of pregnancy on the outcome of breast cancer: a case-control study. Societe Francaise de Senologie et de Pathologie Mammaire Study Group. *Int J Cancer* 1997;**72**: 720-7.

44. Elledge RM, Ciocca DR, Langone G, McGuire WL. Estrogen receptor, progesterone receptor, and HER-2/neu protein in breast cancers from pregnant patients. *Cancer* 1993;**71**: 2499-506.

45. Colleoni M, Rotmensz N, Robertson C, et al. Very young women (<35 years) with operable breast cancer: features of disease at presentation. *Ann Oncol* 2002;**13**: 273-9.

46. Asselin-Labat ML, Vaillant F, Sheridan JM, et al. Control of mammary stem cell function by steroid hormone signalling. *Nature* 2010;**465**: 798-802.

47. Ives A, Musiello T, Saunders C. The experience of pregnancy and early motherhood in women diagnosed with gestational breast cancer. *Psychooncology* 2011.

48. Nugent P, O'Connell TX. Breast cancer and pregnancy. *Arch Surg* 1985;**120**: 1221-4.

49. Zemlickis D, Lishner M, Degendorfer P, et al. Maternal and fetal outcome after breast cancer in pregnancy. *Am J Obstet Gynecol* 1992;**166**: 781-7.

50. Ni Mhuireachtaigh R, O'Gorman DA. Anesthesia in pregnant patients for nonobstetric surgery. *J Clin Anesth* 2006;**18**: 60-6.

51. Moran BJ, Yano H, Al Zahir N, Farquharson M. Conflicting priorities in surgical intervention for cancer in pregnancy. *Lancet Oncol* 2007;**8**: 536-44.

52. Cohen-Kerem R, Railton C, Oren D, Lishner M, Koren G. Pregnancy outcome following non-obstetric surgical intervention. *Am J Surg* 2005;**190**: 467-73.

53. Dominici LS, Kuerer HM, Babiera G, et al. Wound Complications from Surgery in Pregnancy-Associated Breast Cancer (PABC). *Breast Dis* 2010;**31**: 1-5.

54. Gumus N. Severe influence of early pregnancy on newly reconstructed breast. *Breast* 2008;**17**: 429-31.

55. Gentilini O, Cremonesi M, Toesca A, et al. Sentinel lymph node biopsy in pregnant patients with breast cancer. *Eur J Nucl Med Mol Imaging* 2010;**37**: 78-83.

56. Gentilini O, Cremonesi M, Trifiro G, et al. Safety of sentinel node biopsy in pregnant patients with breast cancer. *Ann Oncol* 2004;**15**: 1348-51.

57. Keleher A, Wendt R, III, Delpassand E, Stachowiak AM, Kuerer HM. The safety of lymphatic mapping in pregnant breast cancer patients using Tc-99m sulfur colloid. *Breast J* 2004;**10**: 492-5.

58. Ellner SJ, Hoh CK, Vera DR, Darrah DD, Schulteis G, Wallace AM. Dose-dependent biodistribution of [(99m)Tc]DTPA-mannosyl-dextran for breast cancer sentinel lymph node mapping. *Nucl Med Biol* 2003;**30**: 805-10.

59. Khera SY, Kiluk JV, Hasson DM, et al. Pregnancy-associated breast cancer patients can safely undergo lymphatic mapping. *Breast J* 2008;**14**: 250-4.

60. Cardonick E, Iacobucci A. Use of chemotherapy during human pregnancy. *Lancet Oncol* 2004;**5**: 283-91.

61. Peccatori FA, Azim HA, Jr., Scarfone G, et al. Weekly epirubicin in the treatment of gestational breast cancer (GBC). *Breast Cancer Res Treat* 2009;**115**: 591-4.

62. Amant F, Neven P, Van Calsteren K. Reply on LTE: Treatment of cancer during pregnancy: the need for tailored strategies, by Azim HA and Peccatori FA. *J Clin Oncol* 2010;**28**: e304.

63. Bonilla L, Ben-Aharon I, Vidal L, Gafter-Gvili A, Leibovici L, Stemmer SM. Dose-dense chemotherapy in nonmetastatic breast cancer: a systematic review and meta-analysis of randomized controlled trials. *J Natl Cancer Inst* 2010;**102**: 1845-54.

64. Syme MR, Paxton JW, Keelan JA. Drug transfer and metabolism by the human placenta. *Clin Pharmacokinet* 2004;**43**: 487-514.

65. Lycette JL, Dul CL, Munar M, et al. Effect of pregnancy on the pharmacokinetics of paclitaxel: a case report. *Clin Breast Cancer* 2006;**7**: 342-4.

66. Van Calsteren K, Verbesselt R, Ottevanger P, et al. Pharmacokinetics of Chemotherapeutic Agents in Pregnancy: a Preclinical and Clinical Study . *Acta Obstet Gynecol Scand* 2010;**89**: 1338-45.

67. Rouzier R, Werkoff G, Uzan C, et al. Pregnancy-associated breast cancer is as chemosensitive as non-pregnancy-associated breast cancer in the neoadjuvant setting. *Ann Oncol* 2011.

68. Wiebe VJ, Sipila PE. Pharmacology of antineoplastic agents in pregnancy. *Crit Rev Oncol Hematol* 1994;**16**: 75-112.

69. Germann N, Goffinet F, Goldwasser F. Anthracyclines during pregnancy: embryo-fetal outcome in 160 patients. *Ann Oncol* 2004;**15**: 146-50.

70. Van Calsteren K, Verbesselt R, Beijnen J, et al. Transplacental transfer of anthracyclines, vinblastine, and 4-hydroxy-cyclophosphamide in a baboon model. *Gynecol Oncol* 2010;**119**: 594-600.

71. Van Calsteren K, Verbesselt R, Devlieger R, et al. Transplacental Transfer of Paclitaxel, Docetaxel, Carboplatin, and Trastuzumab in a Baboon Model. *Int J Gynecol Cancer* 2010;**20**: 1456-64.

72. Van Calsteren K, Verbesselt R, Van Bree R, et al. Substantial variation in transplacental transfer of chemotherapeutic agents in a mouse model. *Reprod Sci* 2011;**18**: 57-63.

73. Arceci RJ, Croop JM, Horwitz SB, Housman D. The gene encoding multidrug resistance is induced and expressed at high levels during pregnancy in the secretory epithelium of the uterus. *Proc Natl Acad Sci U S A* 1988;**85**: 4350-4.

74. Smit JW, Huisman MT, van Tellingen O, Wiltshire HR, Schinkel AH. Absence or pharmacological blocking of placental P-glycoprotein profoundly increases fetal drug exposure. *J Clin Invest* 1999;**104**: 1441-7.

75. Gedeon C, Koren G. Designing pregnancy centered medications: drugs which do not cross the human placenta. *Placenta* 2006;**27**: 861-8.

76. Evseenko DA, Paxton JW, Keelan JA. ABC drug transporter expression and functional activity in trophoblast-like cell lines and differentiating primary trophoblast. *Am J Physiol Regul Integr Comp Physiol* 2006;**290**: R1357-R1365.

77. Amant F, Van Calsteren K., Halaska MJ, et al. Gynecologic cancers in pregnancy: guidelines of an international consensus meeting. *Int J Gynecol Cancer* 2009;**19 Suppl 1**: S1-12.

78. Ring AE, Smith IE, Jones A, Shannon C, Galani E, Ellis PA. Chemotherapy for breast cancer during pregnancy: an 18-year experience from five London teaching hospitals. *J Clin Oncol* 2005;**23**: 4192-7.

79. Mir O, Berveiller P, Goffinet F, et al. Taxanes for breast cancer during pregnancy: a systematic review. *Ann Oncol* 2010;**21**: 425-6.

80. Van Calsteren K, Berteloot P, Hanssens M, et al. In utero exposure to chemotherapy: effect on cardiac and neurologic outcome. *J Clin Oncol* 2006;**24**: e16-e17.

81. Garcia-Manero M, Royo MP, Espinos J, Pina L, Alcazar JL, Lopez G. Pregnancy associated breast cancer. *Eur J Surg Oncol* 2009;**35**: 215-8.

82. Giacalone PL, Laffargue F, Benos P. Chemotherapy for breast carcinoma during pregnancy: A French national survey. *Cancer* 1999;**86**: 2266-72.

83. Ebert U, Loffler H, Kirch W. Cytotoxic therapy and pregnancy. *Pharmacol Ther* 1997;**74**: 207-20.

84. Aviles A, Neri N. Hematological malignancies and pregnancy: a final report of 84 children who received chemotherapy in utero. *Clin Lymphoma* 2001;**2**: 173-7.

85. Aviles A, Neri N, Nambo MJ. Long-term evaluation of cardiac function in children who received anthracyclines during pregnancy. *Ann Oncol* 2006;**17**: 286-8.

86. Gnant M, Mlineritsch B, Schippinger W, et al. Endocrine therapy plus zoledronic acid in premenopausal breast cancer. *N Engl J Med* 2009;**360**: 679-91.

87. Levy S, Fayez I, Taguchi N, et al. Pregnancy outcome following in utero exposure to bisphosphonates. *Bone* 2009;**44**: 428-30.

88. Isaacs RJ, Hunter W, Clark K. Tamoxifen as systemic treatment of advanced breast cancer during pregnancy--case report and literature review. *Gynecol Oncol* 2001;**80**: 405-8.

89. Azim HA, Jr., Azim H, Peccatori FA. Treatment of cancer during pregnancy with monoclonal antibodies: a real challenge. *Expert Rev Clin Immunol* 2010;**6**: 821-6.

90. Press MF, Cordon-Cardo C, Slamon DJ. Expression of the HER-2/neu proto-oncogene in normal human adult and fetal tissues. *Oncogene* 1990;**5**: 953-62.

91. Pentsuk N, van der Laan JW. An interspecies comparison of placental antibody transfer: new insights into developmental toxicity testing of monoclonal antibodies. *Birth Defects Res B Dev Reprod Toxicol* 2009;**86**: 328-44.

92. Dale DC, Cottle TE, Fier CJ, et al. Severe chronic neutropenia: treatment and follow-up of patients in the Severe Chronic Neutropenia International Registry. *Am J Hematol* 2003;**72**: 82-93.

93. Rodriguez-Pinilla E, Martinez-Frias ML. Corticosteroids during pregnancy and oral clefts: a case-control study. *Teratology* 1998;**58**: 2-5.

94. Wapner RJ, Sorokin Y, Mele L, et al. Long-term outcomes after repeat doses of antenatal corticosteroids. *N Engl J Med* 2007;**357**: 1190-8.

95. Pavlidis N, Pentheroudakis G. The pregnant mother with breast cancer: diagnostic and therapeutic management. *Cancer Treat Rev* 2005;**31**: 439-47.

96. Petrek JA, Dukoff R, Rogatko A. Prognosis of pregnancy-associated breast cancer. *Cancer* 1991;**67**: 869-72.

97. Tamaru S, Kikuchi A, Takagi K, et al. Neurodevelopmental outcomes of very low birth weight and extremely low birth weight infants at 18 months of corrected age associated with prenatal risk factors. *Early Hum Dev* 2011;**87**: 55-9.

98. Lohaugen GC, Gramstad A, Evensen KA, et al. Cognitive profile in young adults born preterm at very low birthweight. *Dev Med Child Neurol* 2010;**52**: 1133-8.

99. Sorosky JI, Sood AK, Buekers TE. The use of chemotherapeutic agents during pregnancy. *Obstet Gynecol Clin North Am* 1997;**24**: 591-9.

100. Pavlidis N, Pentheroudakis G. Metastatic involvement of placenta and foetus in pregnant women with cancer. *Recent Results Cancer Res* 2008;**178**: 183-94.