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Review

Breast cancer in pregnancy: a literature review

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Abstract

Breast cancer is the most common cancer diagnosed during pregnancy. The incidence of breast cancer in pregnancy (BCP) is expected to increase since women tend to postpone childbearing until later in life and since the incidence of breast cancer increases with age.
The management of this co-incidence is a clinical and ethical multidisciplinary challenge for all involved medical care workers since two lives are at risk. Breast cancer treatment is possible during pregnancy. Still, little prospective research data are available on this condition. In this review, we present an overview of the current knowledge about the safety of diagnostic imaging, staging methods and treatment options of BCP. We also discuss the prognosis, neonatal outcome and recommendations concerning prenatal care.

Key words: Pregnancy, breast, cancer, management, neonatal.

Introduction

80% of all the breast lumps in pregnant women are benign (Byrd *et al.*, 1962). However, any suspicious or persisting mass deserves further investigation.

Breast cancer is the most common malignancy occurring during pregnancy (Van Calsteren *et al.*, 2008). It has been estimated that up to 3% of breast cancers may be diagnosed in pregnant women (White, 1954). The diagnosis of breast cancer in pregnancy (BCP) is expected to become more frequent since there is an increasing trend for women to delay childbearing. Breast cancer incidence increases with age (Loibl *et al.*, 2006).

The diagnosis of cancer in a pregnant woman is a clinical challenge for the mother and the medical team (Teran-Porcayo *et al.*, 2008). The benefit and risks of the different diagnostic and therapeutic modalities should be carefully assessed for both the mother and the fetus. Optimal treatment of the mother must be combined with minimal risk of harm to the fetus.

In this review we aim to highlight the evidence supporting breast cancer treatment during pregnancy. The level of evidence is low since only case reports, small series and mainly retrospective data are available. Therefore, individualisation is mandatory. In any case, breast cancer diagnosis, staging and treatment during pregnancy should adhere as much as possible to standard care.

Diagnosis

The diagnosis of breast cancer in pregnancy is based on clinical examination, histology/cytology and mammography/breast ultrasound (the so-called triple diagnosis), similar to non-pregnant women.

The diagnosis may be delayed and difficult due to physiological changes within the breast during pregnancy (Garcia-Manero *et al.*, 2008). Small masses are difficult to detect and nodularities and densities in the breast are often overlooked or ascribed to benign proliferative changes. Therefore, pregnancy associated breast cancer is usually diagnosed in a higher stage.

In contrast to many other breast cancer cases, BCP is not diagnosed during a screening examination. BCP most often presents in a symptomatic patient.

A painless mass or thickening, occasionally associated with nipple discharge, is most frequently observed (Eedarapalli and Jain, 2006). The clinical examination of the breast at the first prenatal visit is a critical step in the – early – diagnosis of BCP. Although a breast examination at each prenatal visit is unrealistic, an adequate examination is strongly recommended in symptomatic women.

Mammography is diagnostic and enables to detect microcalcifications and multicentricity of masses. With adequate abdominal shielding, a mammography presents little risk to the fetus (Loibl *et al.*, 2006). However, the increased breast vascularity and density and the physiological changes within the breast during pregnancy make the mammogram often difficult to interpret (Hogge *et al.*, 1999), with a considerable false negative rate. *Breast ultrasound* has a high sensitivity and specificity for the diagnosis of BCP (Navrozoglou *et al.*, 2008). It can distinguish between cystic and solid breast lesions (Woo *et al.*, 2003). It is considered the standard method for the evaluation of a palpable breast mass during pregnancy. *Biopsy* of a suspicious mass is the golden standard for the diagnosis of breast cancer (Woo *et al.*, 2003). A fine-needle aspiration (FNAC) can be executed for initial evaluation for cytological investigation. However, sensitivity of cytologic examination during pregnancy is low because atypical cytomorphologic findings are also seen in normal breast tissue during gestation (Sorosky and Scott-Conner, 1998; Novotny *et al.*, 1991). A core needle biopsy is preferred. It is important that the pathologist is informed about the pregnant state to avoid misdiagnosis of the hyperproliferative changes of the breast during gestation.

Similar to non-pregnant women, mainly invasive ductal carcinomas are diagnosed in pregnant women (Parente *et al.*, 1988; Tobon and Horowitz, 1993; King *et al.*, 1985). Since the histopathologic and immunohistochemical findings of BCP are similar to those of non-pregnant young women (Loibl *et al.*, 2006), the age rather than the pregnancy determines breast cancer occurrence.

Staging

Optimal oncological treatment necessitates adequate staging. Some exposure to medical irradiation during pregnancy is therefore unavoidable but should be limited where possible. Ionizing radiation (x-ray) is composed of high-energy photons that are capable of damaging DNA and generating caustic free radicals (Hall, 1991). In general, the expected radiation effects, such as mental retardation and organ malformations, probably only arise above a threshold dose of 0.1-0.2 Gy (Kal, 2005). The dose to the fetus resulting from most conventional radiograph examinations is less than 0.01 Gy. Staging is therefore possible and should be executed when indicated. The risk of not staging is often greater than the potential harm to the fetus. In cases of doubt, the examination is permitted if the result would alter the immediate management (Ring *et al.*, 2005).

A metastatic workup should be limited to patients with high probability of metastasis and only when their establishment may alter therapy (Pereg *et al.*, 2008). Furthermore, the cumulative radiation dose of the required examinations should always be taken into account in the risk assessment of the fetus. The cumulative fetal exposure is calculated in consultation with radiologists and nuclearists. Only the most relevant examinations are performed.

Table 1 gives an overview of the threshold dose of radiation during different stages of pregnancy and the possible adverse effects when exceeding this threshold. Table 2 summarizes the fetal radiation dose due to exposure to several imaging techniques that are discussed below.

Chest radiography with abdominal shielding can be carried out relatively safe during pregnancy. The expected exposure to the fetus ranges from 0 to 0.0001 Gy (Pavlidis and Pentheroudakis, 2005). *Computed tomography* scanning is associated with higher radiation exposure to the fetus. Computed tomography of the upper abdomen with appropriate shielding may be considered safe since it is associated with a fetal exposure of 0.0036 Gy (Osei and Faulkner, 1999). In contrast, the computed tomography scanning of the lower abdomen is less safe since fetal exposure (approximately 0.089 Gy) comes close to the threshold doses.

Controversy continues on the use of *magnetic resonance imaging* (MRI) during pregnancy. The Safety Committee of the Society for MRI stated that 'MRI may be used in pregnant women if other non-ionizing forms of diagnostic imaging are inadequate or if the examination provides important information that would otherwise require exposure to ionizing radiation' (Shellock and Kanal, 1991). However, since the effects of MRI exposure in the prenatal period have not been fully determined, MRI should be used with caution, especially during the first trimester (Oto *et al.*, 2007). The most important fetal concerns are the possibility of teratogenic effects and the potential risk of acoustic damage (Chen *et al.*, 2008). The possible mechanisms of teratogenesis include the heating effect of magnetic resonance gradient changes and direct nonthermal interaction of the electromagnetic field with biological structures. This suggests cautious administration of MRI in the first trimester. The acoustic damage due to the loud noise produced by the MRI scanner coils, appears to be rather a

Table 1. — Overview of adverse effects of radiation and their threshold dose at different stages of gestation (Kal and Struikmans, 2005; ICRP, 2003; UNSCEAR, 1977; Otake *et al.*, 1996; Greskovich and Macklis, 2000; Stovall *et al.*, 1995).

Gestational age (weeks)	Threshold dose of radiation (Gy)	Adverse effect of radiation
2-4 (peri-implantation)	all doses*	prenatal death
5-10 (organogenesis)	0.05-0.2	malformation (in the organs developing at the time of exposure)
10-17	0.06	mental retardation
18-27	0.25	mental retardation
28-birth	0.5	intrauterine growth retardation
0-birth	0.01	childhood cancer and leukaemia**

* the 'all-or-none' phenomenon: radiation will lead either to spontaneous abortion or to healthy survival, depending on the degree of damage of the multipotent embryonic cells at this gestational age.
** an increase from 2-3 (spontaneous incidence) to 3-4 per 1000 (prenatal irradiation) (Kal and Struikmans, 2005).

theoretical than a real concern. Despite the above mentioned concerns, MRI is widely applied during pregnancy, also for non-oncological indications. MRI is of good value for the detection of brain and bone metastases, if clinically indicated (Molckovsky and Madarnas, 2008).

Contrast media are used during radiologic imaging in order to increase diagnostic sensitivity. The intravenous presence of these agents questions fetal safety. After administration of gadolinium or iodinated contrast media during pregnancy, no mutagenic or teratogenic effects have been described (Webb *et al.*, 2005). The most important potential harmful effect of iodinated contrast media within the fetus is the depression of thyroid function. Therefore, it is necessary to check the neonatal thyroid function after delivery. No adverse effects in the fetus have been documented after gadolinium administration during pregnancy. Table 3 gives an overview of the guidelines for the use of iodinated and gadolinium contrast media during pregnancy.

Table 2. — Overview of the fetal dose due to exposure to several imaging techniques, based on our literature search. The threshold dose is 0.01Gy.

Imaging technique	Fetal dose (Gy)
Mammography	0.0000005
Chest x-ray	0-0.0001
CT	
• Upper abdomen	0.0036
• Lower abdomen	0.089
FDG-PET	
• Without CT	0.0106
• With CT	0.0189
Bone scan	0.0008
Lymphatic mapping	0.0043

In recent years, *^{18}fluorodeoxyglucose positron emission tomography (FDG PET)* has become an essential component of cancer management (Zanotti-Fregonara *et al.*, 2008). Limited data on the safety during pregnancy are however available. Also the combined use with computed tomography gains more importance. Zanotti-Fregonara *et al.* described the case of a pregnant patient who underwent ^{18}F-FDG-PET/computed tomography for tumour surveillance. She was found to be pregnant at the time of the examination (embryo age, 8 weeks). The patient received 320 MBq of ^{18}F-FDG. They calculated that the radionuclide dose to the embryo was 10.6 mGy without computed tomography and 18.9 mGy after adding the dose of the unenhanced computed tomography scan. This dose remains within the range of safe levels (Steenvoorde *et al.*, 1998). These data suggest that the embryonal dose in early pregnancy is at least 2 mGy/MBq administered to the mother. Although these data are promising, no conclusions can be made about the safety of FDG-PET during pregnancy based on one case. Further investigations are required.

The low dose *bone scan* exposes the fetus to 0.0008 Gy (Baker *et al.*, 1987). A bladder catheter is inserted to avoid accumulation in the bladder in the proximity of the pregnancy. This examination can therefore be used as an alternative for MRI for the detection of bone metastases of the thoracic or lumbosacral spine (Gwyn and Theriault, 2001).

Sentinel lymph node biopsy (SLNB) has become a valid alternative for standard axillary lymph node dissection in patients with small breast carcinoma and a clinically negative axilla (Veronesi *et al.*, 2003). This procedure is associated with far less serious morbidity than the standard axillary node

Table 3. — Guidelines for the use of contrast media during pregnancy (Webb *et al.*, 2005).

	Iodinated agents	Gadolinium agents
Pregnancy	may be administered in exceptional circumstances, when radiographic examination is essential	may be administered when MRI examination is required
Neonatal care	thyroid function should be checked in the neonate during the 1st week postpartum	no neonatal tests are necessary

dissection (Sener *et al.*, 2001). The use of *lymphoscintigraphy* and SLNB during pregnancy has been considered unsafe for a long time (Gentilini *et al.*, 2004). The sentinel lymph node technique relies on an injection of a radioactive colloid, a vital dye or both in the proximity of the primary lesion (Mondi *et al.*, 2006). There are justifiable concerns regarding the use of any of these agents during pregnancy and the subsequent implications to the developing fetus. However, in 2004, Gentilini *et al.* described that the injected ^{99m}TC sulphur colloid is concentrated only in the injection site and in the lymph nodes with negligible irradiation to other tissues and organs (Gentilini *et al.*, 2004). Only a very small amount of injected activity is circulating in the blood pool and excreted by the urinary system (< 2%). Keleher *et al.* found that the maximum absorbed dose to the fetus in pregnant women undergoing breast lymphoscintigraphy with 92.5 MBq of ^{99m}TC sulphur colloid was 4.3 mGy (Keleher *et al.*, 2004). This is well below the minimum dose reported to be associated with adverse fetal effects. The use of *isosulfan blue* for lymphatic mapping has a possible risk of an allergic or anaphylactic maternal reaction, which can be harmful for the fetus (Khera *et al.*, 2008). Also the maternal life is put into danger since treatment of an anaphylactic reaction during pregnancy is hazardous. There are also some reports of possible skeletal and neurologic defects in rat models (Uren, 2006). Therefore, isosulfan bleu should not be used during pregnancy. Thus, lymphoscintigraphy and SLNB can be performed safely during pregnancy (Gentilini *et al.*, 2004). Radiocolloid mapping is the preferred method (Khera *et al.*, 2008). By minimising surgical treatment, it will decrease surgical morbidity and reduce the period op postoperative recovery, similar to non-pregnant women.

Surgical management

Treatment modalities for BCP should take into account two lives. The treatment strategy must integrate the physical and emotional well being of the mother with the fetal health (Rosenkranz and Lucci, 2005/6). Treatment should adhere as closely as possible to standardised protocols for patients without concomitant pregnancy (Garcia-Manero *et al.*, 2008). The major goal of BCP-treatment is local control of the disease and prevention of systemic metastases (Loibl *et al.*, 2006). It is important that treatment is not delayed unless the woman is within 2-3 weeks of delivery (Jones, 2006). Breast surgery can safely be performed during all trimesters of pregnancy with minimal risk to the developing fetus (Duncan *et al.*, 1986). Both radical modified mastectomy and breast conserving surgery with axillary or sentinel lymph node dissection can be carried out in the treatment of local disease (Navrozoglou *et al.*, 2008). The major difference between these two options is the need for radiotherapy after the breast conserving treatment to avoid local recurrence. However, in this age group, chemotherapy is usually indicated. As a result, radiotherapy can be administered after delivery (Ring, 2007). As described below, there is evidence that radiotherapy could probably be safely administered during the first and second trimester of gestation. Therefore, breast conserving therapy plays a substantial role in the treatment of BCP, similar to the non-pregnant woman with breast cancer. Multidisciplinary input from surgeons, anaesthesiologists and obstetricians is essential to ensure fetal and maternal wellbeing throughout the perioperative period (Mhuireachtaigh and O'Gorman, 2006). Perioperative events leading to severe maternal hypotension or hypoxemia pose the greatest risk to the fetus. Therefore, fetal wellbeing is best ensured by careful maintenance of stable maternal hemodynamic parameters and oxygenation.

Radiotherapy

There exists some controversy regarding the safety of radiation therapy during pregnancy. In general, fetal exposure depends on several factors including the target dose, size of radiation field, and the distance from the edges of the field to the fetus. According to the 'International recommendations from an expert meeting', external beam radiation necessary for the completion of breast conservation or postmastectomy radiation is contraindicated during

Table 4. — Total radiation dose to conceptus, resulting from tangential breast irradiation at the first, second, and third trimesters of gestation (Mazonakis *et al.*, 2003).

Field size (cm^2)	Conceptus dose (cGy)		
	First trimester	Second trimester	Third trimester
4.5 × 11.0	2.1-2.9	2.2-7.5	2.2-16.8
6.0 × 12.5	2.8-3.9	2.9-10.4	3.3-23.8
8.0 × 14.0	3.5-5.1	3.7-13.9	4.0-34.7
10.0 × 16.0	4.4-6.2	4.7-18.2	5.0-45.2
11.5 × 18.0	5.2-7.6	5.9-24.6	6.5-58.6

Note: Conceptus dose values correspond to a tumour dose of 50 Gy.

pregnancy because of the risks associated with fetal exposure to radiation (Loibl *et al.*, 2006). However, successful radiotherapy of breast cancer during pregnancy and birth of healthy children have been reported (Van der Giessen, 1997; Ngu *et al.*, 1992; Antypas *et al.*, 1998). According to these and other findings, Kal *et al.* concluded that radiotherapy of pregnant patients with breast cancer is possible with fetal doses below the deterministic threshold (Kal and Struikmans, 2005).

Mazonakis *et al.* studied the conceptus dose resulting from tangential breast irradiation using anthropomorphic phantoms simulating the geometry of a pregnant woman at the first, second and third trimester of gestation (Mazonakis *et al.*, 2003). As expected, the conceptus dose increased as the pregnancy became more advanced, because of the increased proximity of the fetus to the primary irradiation field. Table 4 gives an overview of the radiation dose to the fetus according to the gestational stage, based on their findings. These data are applicable for all the X-ray energies from 4 to 10 MV used for breast radiotherapy. They concluded that during the first and the second trimester of pregnancy, the fetal irradiation dose is considerably smaller than the threshold values associated with adverse fetal effects. During the third trimester, however, the conceptus dose seems to exceed this threshold. They also noticed that in utero irradiation at all gestational ages may increase the risk of cancer induction during childhood. These data could be used to estimate the conceptus dose from breast radiotherapy and allow the quantification of the fetal radiation risks. According to these findings, the use of radiotherapy would be safe during the first and the second trimester of pregnancy, but during the third trimester radiotherapy should be avoided.

Systemic cancer treatment

Based on breast cancer tumour biology in young women, chemotherapy is mostly necessary for BCP. Cytotoxic agents are minimally selective and usually affect rapidly proliferating cells (Blatt *et al.*, 1980; Zemlickis *et al.*, 1992). As a rapid rate of cell division characterizes the fetal state, it is predictable that the fetus would be especially sensitive to the effects of anticancer drugs (Barber, 1981).

The use of chemotherapy during the first trimester increases the risk of spontaneous abortion, fetal death, and major malformations according to gestational age at exposure (Doll *et al.*, 1989; Zemlickis *et al.*, 1992). The phase of organogenesis (2-8 weeks) is likely to be the most vulnerable phase of gestation (Amant *et al.*, 2008). Administration of chemotherapy during this stage is contraindicated and should be postponed. After organogenesis, several organs including the eyes, genitalia, hematopoietic system and the central nervous system (CNS) remain vulnerable to chemotherapy (Cardonick and Iacobucci, 2004). Therefore, it is strongly recommended to wait until 14 weeks duration to initiate cytotoxic treatment (Amant *et al.*, 2008). During the second and third trimester, chemotherapy can be administered relatively safely (Cardonick and Iacobucci, 2004), even though it is recognised that many cytotoxic drugs do cross the placenta (Jones, 2006). However, an increased risk for intrauterine growth retardation and low birth weight has been associated with in utero exposure to cytotoxic drugs (Zemlickis *et al.*, 1992).

The decision to use chemotherapy during pregnancy should be weighed against the effect of treatment delay on maternal survival (Pereg *et al.*, 2008). If possible, chemotherapy should be postponed until the end of the first trimester. If breast cancer is diagnosed in the late third trimester, adjuvant chemotherapy may be administered postpartum (Navrozoglou *et al.*, 2008). However, the daily increased risk for developing axillary metastasis for an untreated breast carcinoma in pregnant women is 0.057% (Nettleton *et al.*, 1996). This estimation is lower in surgically treated patients, but definitely not negligible.

Cyclophosphamide and doxorubicin, with or without 5-fluorouracil, is the preferred combination during pregnancy (Cardonick and Iacobucci, 2004). Anthracyclins are judged to be relatively safe, but there are still concerns of anthracyclin-associated fetal cardiotoxicity (Lenhard *et al.*, 2008). Regarding the cardiotoxic risk, there is one study in which echocardiograms were performed every second week in pregnant women undergoing treatment with doxorubicin and cyclophosphamide (Meyer-Wittkopf *et al.*, 2001). The fetus was monitored beginning at the 24th gestational week and data were compared to untreated healthy mothers at 20th to 40th weeks of pregnancy. Neither short-term results for systolic function nor 2-year follow up for myocardial damage showed a significant difference between both study groups. In another study, Aviles *et al.* described 81 cases of in utero exposure to anthracyclins (Aviles *et al.*, 2006). The children underwent a clinical and echocardiographic examination every 5 years. After a mean follow up of 17.1 years (9.3-29.5 years) normal echocardiographic findings and a normal ejection fraction were observed. However, the possibility of cardiac disease later in life, due to prenatal anthracyclin exposure of the developing myocardium, can not be excluded (Meyer-Wittkopf *et al.*, 2001). Cardonick *et al.* concluded that the use of doxorubicin is preferred during pregnancy and they do not recommend the use of epirubicin (Cardonick and Iacobucci, 2004). This is based on one study where 23 % of cases exposed to epirubicin died either as fetuses or as neonates. However, Peccatori *et al.* described the administration of anthracyclin-containing regimens to 11 pregnant women with breast cancer (Peccatori *et al.*, 2004). All patients were treated after 15 weeks of gestation. Six patients received epirubicin once a week for 10-16 weeks until delivery, 5 patients received epirubicin once every 3 weeks and 2 patients were given doxorubicin-containing regimens. No severe maternal or fetal complications were seen. These data suggest that epirubicin could also be safely administered during pregnancy.

The role of taxanes in pregnancy is still unclear (Lenhard *et al.*, 2008). The data for the use of taxanes are mainly based on case reports and are therefore not meaningful to support its safety. There are data postulating paclitaxel to be safe after the first trimester, as it can be bound by drug-extruding transporters like P-glycoprotein (Pgp) or BCRP-1, with a high placental expression (Arceci *et al.*, 1988). Pgp is an efflux transporter for various xenobiotics which is highly expressed on the maternal compartment of the placenta (Gedeon and Koren, 2006). Absence or pharmacological blocking of placental PgP profoundly increases fetal drug exposure (Smit *et al.*, 1999). The placental Pgp is postulated to reduce transplacental transfer of taxanes, making their clinical use possible during the second and third trimester of gestation (Mir *et al.*, 2008). Mir *et al.*, for example, found 9 case reports documenting the use of paclitaxel (Sood *et al.*, 2001; Mendez *et al.*, 2003; Gaducci *et al.*, 2003; Gonzalez-Angulo *et al.*, 2004; Bader *et al.*, 2007; Mantovani *et al.*, 2007; Lycette *et al.*, 2006; Hubalek *et al.*, 2007; Modares-Gilani *et al.*, 2007) and 6 cases with administration of docetaxel (De Santis *et al.*, 2000; Gainford and Clemons, 2006; Potluri *et al.*, 2006; Nieto *et al.*, 2006; Sekar and Stone, 2007) during the second and third trimester of pregnancy; no malformations were reported. However, further investigation is warranted.

Pharmacokinetic and pharmacodynamic profiles are altered in pregnancy (Mhuireachtaigh and O'Gorman, 2006). The increased blood volume and renal clearance might decrease active drug concentrations (Cardonick and Iacobucci, 2004). A faster hepatic mixed-function oxidase system might also lower drug concentrations, and changes in gastrointestinal function can affect drug absorption. In pregnancy, there is a physiologic hypoalbuminemia, increasing the amount of unbound active drug. However, oestrogen is likely to increase other plasma proteins, which might decrease active drug fractions. In addition, the amniotic fluid can act as third space for some drugs (Amant *et al.*, 2008).

Since various pharmacokinetic effects occur during gestation, it is very difficult to predict the actual drug concentration. Therefore, until more data are available, the current dosage of the chemotherapeutic agents is equal for pregnant compared to non-pregnant women and is based on height and weight (Amant *et al.*, 2008). However, there is evidence that doxorubicin administration during pregnancy results in a lower drug exposure and decreased tissue toxicity (Van Calsteren *et al.*, 2007). Van Calsteren *et al.* described a 32-year-old gravida who received 3 cycles of doxorubicin-cyclophosphamide, during and after pregnancy. Blood samples were collected at the gestational age of 24 and 30 weeks and 4 and 7 weeks postpartum. They found a reduced area under the curve and half life of doxorubicin, an increased clearance and distribution volume. These data are in line with the physiological changes during pregnancy. In addition, they noticed less tissue toxicity since thrombocytopenia only was noted after and not during pregnancy. A single case is however insufficient to draw firm conclusions and further research is necessary. Two critical steps must be taken into account: (a) if there is an actual decrease in tissue toxicity during pregnancy and (b) whether the decreased toxicity will result in a worse overall prognosis.

Supportive treatment for chemotherapy can be given mainly according to the general recommendations (Gralla *et al.*, 1999). Regarding the use of corticoids, methylprednisolone or hydrocortisone are extensively metabolized in the placenta and little crosses into the fetal compartment. They are therefore preferred over dexa- or betamethasone (Blanford and Murphy, 1977). Repeated antenatal exposure to dexa/betamethasone resulted in animal models in decreased body and brain weight, delay in the maturation time-table and hormonal disturbances (Aghajafari *et al.*, 2002; de Vries *et al.*, 2007). This concern was raised subsequently in the National Institutes of Health Consensus (Antenatal corticosteroids revisited: repeat courses, 2000). More children with attention problems and higher rates of cerebral palsy have been described (Crowther *et al.*, 2007; Wapner *et al.*, 2007).

Granulocyte colony-stimulating factor (G-CSF) and erythropoetin have been used safely in pregnant patients and their use should follow current guidelines for growth factor support during chemotherapy (Ozer *et al.*, 2000).

Trastuzumab (Herceptin®) is a monoclonal antibody directed against the human epidermal growth factor receptor 2 protein (HER-2), a member of the epidermal growth factor receptor family (Shrim *et al.*, 2007). HER-2 is known to play an important role in embryonic development (Lee *et al.*, 1995). There is little information about the use of trastuzumab during pregnancy (Lenhard *et al.*, 2008). In the literature, there are a few cases of in utero exposure. The administration of trastuzumab during pregnancy is associated with oligo- or anhydramnios (Watson, 2005; Fanale *et al.*, 2005; Bader *et al.*, 2007; Witzel *et al.*, 2008). Possibly, the presence of the HER-2 protein in the fetal renal-tubule epithelial cells (and not in adult kidneys) can explain a decreased function (Wilson *et al.*, 2006). However, delivery of a healthy baby has also been reported (Waterston and Graham, 2006; Shrim *et al.*, 2007). The altered renal function and unknown long-term impact in the offspring suggest limiting the use of trastuzumab during pregnancy (Amant *et al.*, 2008). In addition, HER-2 appears to be critical to neural and cardiac development (Lee *et al.*, 1995). Evaluation of the mechanisms of action of the HER-2 protein in human fetal development is required and may shed further light on our understanding of safety and treatment options during pregnancy (Shrim *et al.*, 2007).

Tamoxifen is a nonsteroidal selective estrogen receptor modulator and is currently used as the adjuvant endocrine treatment of choice for premenopausal women treated for hormone sensitive breast cancer. Its potential for causing fetal harm during pregnancy remains inconclusive (Berger and Clericuzio, 2008). Neonatal defects from tamoxifen have been described in the genital tract in female mice (Cunha *et al.*, 1987) and there are reports of birth defects such as Goldenhar syndrome (oculoauriculovertebral dysplasia) (Cullins *et al.*, 1994) and ambiguous genitalia (Tewari *et al.*, 1997) in children born to women exposed to tamoxifen. Berger *et al.* described a case of tamoxifen exposure during the first trimester of pregnancy, associated with Pierre Robin sequence, defined as the triad of small mandible, cleft palate and glossoptosis (Berger and Clericuzio, 2008). In contrast, Clark reported no fetal abnormalities in women who became pregnant while on tamoxifen for breast carcinoma prevention (Clark, 1993). This suggests that the use of tamoxifen is not necessarily associated with fetal harm.

However, to date, tamoxifen is not recommended during pregnancy and hormone treatment, if indicated, should be started after delivery and after completion of chemotherapy (Loibl *et al.*, 2006).

Table 5 gives an overview of the therapeutic options during the different stages of pregnancy, based on our literature review.

Prognosis

When the diagnosis of BCP is established, it is regularly questioned whether continuing the pregnancy will adversely affect the prognosis of the mother (Jones, 2006). There has been a concern that the hormonal milieu of pregnancy contributes to the development and progression of the breast malignancy (Hahn *et al.*, 2006). However, the majority of pregnant women with breast cancer seem to have estrogen and progesterone receptor-negative tumours. The prognosis of pregnant women with breast cancer stage-for-stage is equivalent to that of their non-pregnant counterparts (Zemlickis *et al.*, 1992; Reed *et al.*, 2003) since it is determined by pregnancy independent cancer characteristics. In a retrospective, population-based cohort study, Stensheim *et al.* tried to assess if cancers diagnosed during pregnancy and lactation were associated with an increased risk of cause-specific death (Stensheim *et al.*, 2009). They found no increased risk of cause-specific death in women diagnosed with breast cancer during pregnancy. Therefore, termination of pregnancy is unlikely to improve the maternal outcome.

However, if a woman is diagnosed with breast cancer during the first trimester of pregnancy, the risk of delaying treatment need to be considered and therapeutic abortion may be preferable (Molckovsky and Madarnas, 2008). Similarly, women who present with very aggressive or very advanced disease need to be informed of their prognosis in order to make an informed choice regarding their pregnancy

Table 5. — Overview of the therapeutic options during the different stages of pregnancy.

Stage of pregnancy	Therapeutic options
1st trimester	– surgery – radiotherapy
2nd trimester	– surgery – radiotherapy – chemotherapy
3rd trimester	– surgery – chemotherapy

(Pavlidis and Pentheroudakis, 2005). To a certain extent, termination of pregnancy is a personal decision made by the pregnant woman herself or by the couple (Navrozoglou, 2008) after profound medical and emotional counselling.

Neonatal and long-term outcome

The majority of information on the effects of in utero exposure to chemotherapy has been derived from retrospective case reports and series (Gwyn, 2005). For the newborn, early and reversible toxicities secondary to cytotoxic treatment of malignancies in a pregnant woman are principally anemia, neutropenia and alopecia, and these are dependent on the timing of the therapy in relation to delivery (Maghfoor and Doll, 2001). Additionally, low birth weight has been reported either as a result of intrauterine growth retardation or as a result of premature labour (Pavlidis and Pentheroudakis, 2005). A meta-analysis concluded that the use of chemotherapy during the second and third trimester is not associated with an increase of congenital abnormalities (Cardonick and Iacobucci, 2004). The potential for long-term sequelae from in utero chemotherapy exposure remains a major concern. The fact that the central nervous system continues to develop throughout gestation raises concerns regarding long-term neurodevelopmental outcome of children exposed to in utero chemotherapy (Pereg *et al.*, 2008). Other concerns are childhood malignancy and long-term fertility. Information regarding these issues is limited due to difficulties in long-term follow-up and the relative rarity of such cases. However, there seems to be no increased risk of developing childhood malignancies compared to the general population. The limited available data suggest that chemotherapy does not have a major impact on later neurodevelopment. The data should however be interpreted cautiously since the methodology is questionable or biased.

Aviles *et al.* performed a cross-sectional study of pregnant women with hematologic malignancies and examined the outcomes of 84 children exposed to chemotherapy in utero (Aviles and Neri, 2001). They found that the children's learning and educational performance were normal and no congenital, neurologic, psychologic, cardiac, or cytogenetic abnormalities or malignancies were noted. Furthermore, the second-generation children were reported to have no significant problems, although their parents refused formal medical or intelligence tests for their children. However, it seems unlikely that no health problems at all were found in all of the 84 children. The methodology from this study needs to be questioned. Hahn *et al.* described a series of 57 pregnant breast cancer patients who were treated on a single-arm, multidisciplinary, institutional review board-approved protocol with FAC (5-fluorouracil, doxorubicin, cyclophosphamide) in adjuvant or neoadjuvant setting (Hahn *et al.*, 2006). Parents/guardians were surveyed by mail or telephone regarding outcomes of children exposed to chemotherapy in utero. Most of the children were exposed to chemotherapy in the second trimester. At the time of the survey, the children's ages ranged from 2 to 157 months. The majority of children did not have any significant neonatal complication. Although this information is important, no clinical or technical examination was performed and the results might be biased by the parental opinion. Van Calsteren *et al.* described a multicenter prospective study, concerning the effect of in utero exposure to chemotherapy on cardiac and neurologic outcome (Van Calsteren *et al.*, 2006). They recruited women from four different Belgian centres, who received chemotherapy during pregnancy and all children were invited for a full neurologic and cardiologic assessment. They found that neonatal morbidity after intrauterine exposure to cytotoxic drugs mainly appears to be related to prematurity. No developmental problems were seen, however, a tendency towards a thinner ventricular wall was found. This is an important finding since chemotherapy may interfere with cardiac development. However, this systematic assessment only included 10 children.

It is clear that additional and preferably prospective collection of data of children exposed to chemotherapy in utero is warranted. This information is important to guide future management of pregnant cancer patients and to provide parents and their children with information on short- and long-term complications of exposure to chemotherapy in utero.

Prenatal care

Prenatal care in women diagnosed with breast cancer during pregnancy should be performed like in other pregnant women (Lenhard *et al.*, 2008). It is

important to estimate correctly the fetal risk caused by the mother's cancer treatment. Therefore, before starting treatment, an ultrasound of the fetus should be performed to ensure that the fetus is normal and to clearly define the gestational age and date of delivery (Loibl *et al.*, 2006). Before every cycle of chemotherapy, an evaluation of fetal growth must be carried out.

The time of delivery should be balanced according to the need of breast cancer treatment and the maturation of the fetus (Lenhard *et al.*, 2008). Premature delivery should best be avoided and delivery after 35 weeks should be aimed for (Van Calsteren *et al.*, 2007). The mode of delivery is determined by obstetrical indications. If further chemotherapy is necessary, vaginal delivery is recommended because of lower risk of therapy delay due to lower maternal morbidity (Lydon-Rochelle *et al.*, 2000). Delivery should occur 3 weeks after the last dose of anthracyclin-based chemotherapy to allow the bone marrow to recover and to minimize the risk of maternal and fetal neutropenia (Loibl *et al.*, 2006). Furthermore, neonates, especially preterm babies, have limited capacity to metabolize and eliminate drugs due to liver and renal immaturity. The delay of delivery after chemotherapy will allow fetal drug excretion via the placenta (Sorosky *et al.*, 1997). Therefore, chemotherapy should not be given after 35 weeks of gestation. The first dose of chemotherapy should be given once the mother is recovered from delivery. Although placental metastases in breast cancer are rare, the placenta should be analysed histopathologically after delivery (Alexander *et al.*, 2003; Dunn *et al.*, 1999).

Conclusion

Breast cancer is the most common malignancy occurring during pregnancy. The most important aspect associated in BCP is the fact that two lives are at risk. Therefore, a proposed plan of care must integrate the physical and emotional well being of the mother with the health of the fetus. The diagnosis of BCP is based on clinical examination, breast ultrasound/mammography (with adequate abdominal shielding) and histology/cytology, similar to non-pregnant women. To obtain optimal maternal treatment, an adequate staging is mandatory. With secure protection, staging examinations can be performed safely during pregnancy. However, the cumulative radiation dose must always be taken into account. The treatment of BCP should adhere as closely as possible to standardised protocols. Breast cancer surgery can safely be performed during all trimesters of pregnancy with minimal risk to the fetus. Although there remains some controversy about its safety, radiation therapy could be performed safely during the first and second trimester of pregnancy. Chemotherapy can safely be administered during the second and third trimester. Cyclophosphamide and doxorubicin, with or without 5-fluorouracil, is the preferred combination. To date, the use of trastuzumab and tamoxifen during pregnancy is not recommended. Per stage the prognosis for BCP seems to be similar to non-pregnant women provided the same treatment is administered. Neonatal morbidity mainly appears to be related to prematurity. Therefore, premature delivery should be avoided. There are only a few reports about short- and long-term neonatal outcome, but so far they are reassuring. It is clear that additional information is warranted. Further investigation and prospective studies are important to guide optimal management of pregnant cancer patients and to provide parents and their children with accurate information. Such a study project recently has been initiated (www.cancerinpregnancy.org). Centralisation of information is crucial when clinical important information on an uncommon disease entity is aimed for. The investigators focus on maternal care and outcome. In addition, special attention is paid on the long term outcome of children who were in utero exposed to cytotoxic treatment. Participation to these initiatives is necessary since pregnant cancer patients deserve optimal care.

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