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## Review

## Breast cancer in pregnancy: Recommendations of an international consensus meeting <sup>☆</sup>

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## ABSTRACT

**Purpose:** To provide guidance for clinicians about the diagnosis, staging and treatment of breast cancer occurring during an otherwise uncomplicated pregnancy.

**Methods:** An international expert Panel convened to address a series of questions identified by a literature review and personal experience. Issues relating to the diagnosis and management of breast cancer after delivery were outside the scope.

<sup>☆</sup> The organisation of the consensus meeting was endorsed by the European Society of Gynecological Cancer.

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Surgery  
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**Results:** There is a paucity of large and/or randomized studies. Based on cohort studies, case series and case reports, the recommendations represent the best available evidence, albeit of a lower grade than is optimal.

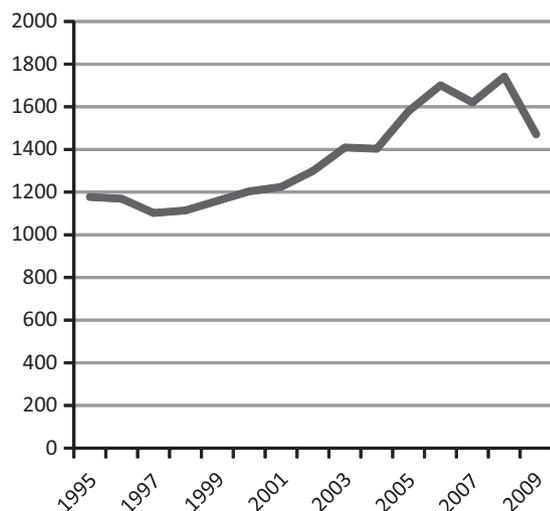
**Recommendations:** In most circumstances, serious consideration should be given to the option of treating breast cancer whilst continuing with the pregnancy. Each woman should ideally be referred to a centre with sufficient expertise, given a clear explanation of treatment options. Most diagnostic and staging examinations can be performed adequately and safely during pregnancy. Treatment should however be adapted to the clinical presentation and the trimester of the pregnancy: surgery can be performed during all trimesters of pregnancy; radiotherapy can be considered during the first and second trimester but should be postponed during the third trimester; and standard chemotherapies can be used during the second and third trimester. Since neonatal morbidity mainly appears to be related to prematurity, delivery should not be induced before 37 weeks, if at all possible.

**Conclusions:** The treatment of breast cancer in pregnancy should be executed by experienced specialists in a multidisciplinary setting and should adhere as closely as possible to standard protocols.

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## 1. Introduction

Breast cancer is the most common malignancy occurring during pregnancy.<sup>1</sup> Approximately 1 in 3000 pregnancies is associated with cancer.<sup>2</sup> 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.<sup>3</sup> The situation is complex since maternal treatment is essential though possibly harmful to the foetus. There is generally limited experience in treating this clinical setting of breast cancer and some may be reluctant to take the challenge. This may lead to, delayed or under-treatment of the breast cancer, or premature delivery and/or termination of the pregnancy. The increased awareness of the potential to treat cancer during pregnancy is associated with a growing number of scientific reports on this topic (Fig. 1). The purpose of this guideline is to review the literature on the safety and accuracy



**Fig. 1 – Number of PubMed publications containing ‘cancer’ and ‘pregnancy’ per year.**

of diagnosis, staging methods and treatment options of BCP. The guideline is restricted to breast cancer diagnosed during an otherwise uncomplicated pregnancy. Breast cancer diagnosed after delivery is not included.

## 2. Methods

Articles were identified during a PUBMED search looking for key-words including pregnancy, breast cancer, diagnosis, staging, management, surgery, radiotherapy, chemotherapy, prognosis and neonatal outcome. In the absence of any randomised trial, study designs reviewed included cohort series, case series and case reports. Pre-clinical studies were restricted to those relating to transplacental transport of cytotoxic drugs. The search did not extend to anaesthesiology, supportive treatment for chemotherapy and psychosocial/ethical concerns as they had been covered during a previous consensus meeting on gynaecological cancer during pregnancy.<sup>4</sup> A manuscript summarising and interpreting the literature was constructed. A first draft and a CD containing the 155 identified articles were sent to the Panel members to prepare discussion. The Panel members were invited based on their research and expertise, including clinical pharmacology, gynaecological oncology, medical oncology, nuclear medicine, obstetrics, paediatrics, radiology and radiation oncology. Experts from 8 European countries were identified and were specifically asked to review those aspects for which they had the most experience. They supplemented the evidence base with hand searched articles. Their contributions and comments were incorporated, resulting in a revised guideline, which was then discussed with all Panel members at a face-to-face meeting on the 21st of January 2010 in Leuven, Belgium. A third version was then drafted and reviewed iteratively over the subsequent 2 months amongst all Panel members, all of whom could comment on any aspect of the document. All Panel members have agreed with the final recommendations and consensus document.

### 3. Results

#### 3.1. How should breast cancer during pregnancy be diagnosed?

Similar to non-pregnant women, the diagnosis of breast cancer in pregnancy is based on clinical examination, histology, mammography and breast ultrasound with or without magnetic resonance imaging (MRI). The diagnosis is difficult and often delayed resulting in later stage presentation due to pregnancy related physiological changes.<sup>5</sup> Average delay of the diagnosis from the first symptoms ranges from 1 to 2 months.<sup>6</sup> Delay of diagnosis during pregnancy by one month may increase the risk of nodal involvement by 0.9%.<sup>7</sup> Therefore, a breast mass persisting for longer than 2–4 weeks should be taken seriously. The Panel believes that the diagnosis of BCP should focus on history, clinical examination, imaging, pathology and less common presentations of BCP.

##### 3.1.1. History

History taking, including an assessment of risk factors, is warranted, as in non-pregnant women. Women (48%) with an early-onset of breast cancer have a positive family history and 9% were associated with BRCA 1 or BRCA 2 mutations.<sup>8</sup> Other studies report 2–29% of young patients with breast cancer to be BRCA positive.<sup>9</sup> Therefore, genetic counselling should be considered. Patients with a prior diagnosis of (pre)cancerous lesions deserve close follow-up.

##### 3.1.2. Clinical presentation

BCP most often presents as a painless, palpable mass in a symptomatic patient. Rarely a bloodstained nipple discharge is observed.<sup>10</sup> Every suspicious mass should be fully investigated with a complete diagnostic work-up.

##### 3.1.3. Mammography, breast ultrasound, magnetic resonance imaging

Breast imaging during pregnancy requires particular expertise since the physiological changes, including increased breast vascularity and density, render imaging modalities more difficult to interpret. Breast ultrasound has a high sensitivity and specificity for the diagnosis of BCP.<sup>11</sup> It can distinguish between cystic and solid breast lesions.<sup>6</sup> It is the standard method for the evaluation of a palpable breast mass during pregnancy. With adequate abdominal shielding, a mammography presents little risk to the foetus.<sup>3</sup> The Panel's recommendation is to start with one oblique view. When a suspicious mass is noted, both craniocaudal and mediolateral oblique views of both breasts are needed to exclude multicentric and bilateral disease. MRI may be used in pregnant women if other non-ionising forms of diagnostic imaging are inadequate or if the examination provides important information that would otherwise require exposure to ionising radiation (Safety Committee of the Society guidelines for MRI).<sup>12</sup> However, given that 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.<sup>13</sup> No results of breast MRI specificity and sensitivity in pregnant patients have yet been reported. Gadolinium adds

to sensitivity and specificity but crosses the placenta resulting in high fetal concentrations.<sup>14</sup> Gadolinium is associated with nephrogenic systemic fibrosis in adults with an impaired kidney function. Children under 1 year are considered at low-risk to develop nephrogenic systemic fibrosis, because of their immature renal function. If needed, preference should be given to Gadobenate dimeglumine (Multihance<sup>®</sup>) and Gadoterate meglumine (Dotarem<sup>®</sup>) contrast media since no unconfounded cases of nephrogenic systemic fibrosis have been reported with these agents.

##### 3.1.4. Pathology

Biopsy of a suspicious mass is the gold standard for the diagnosis of breast cancer.<sup>6</sup> A core needle biopsy is the technique of choice. The sensitivity of core needle biopsy is around 90%.<sup>15</sup> Fine Needle aspiration cytology (FNAC) may be misleading and should not be performed during pregnancy. The pathologist must be made aware of the pregnancy to avoid misdiagnosis of hyperproliferative changes of the breast during gestation. The predominant histology type in pregnant women is invasive ductal carcinoma.<sup>16–18</sup> As in age-matched young women the tumours during pregnancy are more often oestrogen and progesterone receptor negative and HER-2/*neu* positive. Age, rather than the pregnancy appears to determine the biologic features of the tumour.<sup>3,19</sup> Therefore, pregnancy itself should not be regarded as a poor-prognostic indicator.<sup>19–21</sup>

##### 3.1.5. Less common presentations of BCP

Bloody nipple discharge from a single duct should be explored with mammography and ultrasound. Ductogram, ductoscopy and cytology lack sensitivity and specificity. However, postponing treatment until after delivery of intraductal papilloma (with or without ductal carcinoma in situ), provided there is no evidence of an invasive component, is unlikely to alter the prognosis.

In case of oedema or inflammatory signs, a single course of antibiotic treatment should be performed. If there is no resolution and in the absence of a mass, a skin biopsy should be performed to differentiate inflammatory breast cancer from other benign conditions.

#### 3.2. How should a pregnant breast cancer patient be staged?

The Panel believes that staging procedures, including radiology, should always be executed if they are likely to change the therapeutic decision and clinical practice. Ionising radiation is composed of photons that are capable of damaging DNA directly or by the generation of caustic free radicals.<sup>22</sup> However, threshold related deterministic radiation effects, such as mental retardation and organ malformations, only arise above a threshold dose of 0.1–0.2 Gy.<sup>23</sup> This is significantly higher than the dose resulting to the foetus from the most conventional radiographic examinations, which are usually well below 0.01 Gy. In Table S1 an overview is given of the threshold dose of radiation during different stages of pregnancy and the possible adverse effects of exceeding this threshold. In Table S2, an overview of the fetal dose due to exposure to several imaging techniques is presented. Organ

malformations of radiation exposition below the threshold doses have not been reported. Moreover, repetitive low doses (as in case of diagnostic work-up) are considered less damaging than one single exposure to the same total dose. However, subtle possible long term effects including cancer or genetic damage of the offspring can be expected even with the lowest doses of ionising radiation, which requires the radiation dose to be kept ‘as low as reasonably achievable’. The Panel believes that it is important that radiologists and nuclear medicine physicians estimate the cumulative toxicity which will permit selection of the most relevant examinations, and tailor the procedures to the individual patient. Therefore, a staging strategy for every individual patient should be discussed and planned at a multidisciplinary setting.

Since lungs, bone and liver are the commonest sites of metastatic disease, these organs should undergo staging procedures including chest X-ray, liver ultrasound, bone scanning and/or MRI if the risk of discovering metastases is sufficiently high. If this risk is low, distance disease staging should be postponed to after delivery. Chest radiography with abdominal shielding to detect pulmonary metastasis can be carried out safely during pregnancy. Liver ultrasound is the preferred technique to detect liver metastases. MRI could be used if additional information is needed. MRI is also preferred to detect bone metastasis since it is not associated with radiation and contrast agents are not needed. Bone scan is only recommended in cases of uncertain MRI findings, or when MRI is unavailable. Simple but effective precautions may significantly decrease radiation dose: such as the placement of a bladder catheter or injecting a lower tracer dose (e.g. half the dose compensated by a doubled acquisition time). Sentinel lymph node biopsy (SLNB) for staging of the regional lymph nodes can be performed safely during pregnancy.<sup>24,25</sup> It is advisable to inject colloid in the morning (1-d protocol) to reduce the time and dose of radiation. Blue dye should not be used during pregnancy. Its use has a possible risk of an allergic or anaphylactic maternal reaction, which can be harmful for the foetus.<sup>26</sup> Until now, there is no indication for positron emission tomography in breast carcinoma during pregnancy.

### 3.3. What options are there for the management of breast cancer during pregnancy?

Maternal treatment should adhere as closely as possible to standardised protocols for patients without concomitant pregnancy. It is important that treatment is not delayed unless the delivery is already planned within the next 2–4 weeks.<sup>27</sup> In Table 1 an overview is given of the therapeutic options during the different stages of pregnancy. An algorithm for the treatment of BCP is shown in Fig. 2. When BCP is diagnosed in the first trimester, each woman should have the option to terminate pregnancy, after careful counselling and information about all aspects.

#### 3.3.1. Surgery

The Panel recognises that there is an extensive experience with surgery during pregnancy. Multidisciplinary input from breast surgeons, anaesthesiologists and obstetricians is essential to ensure fetal and maternal wellbeing throughout

**Table 1 – Therapeutic options during the different stages of pregnancy.**

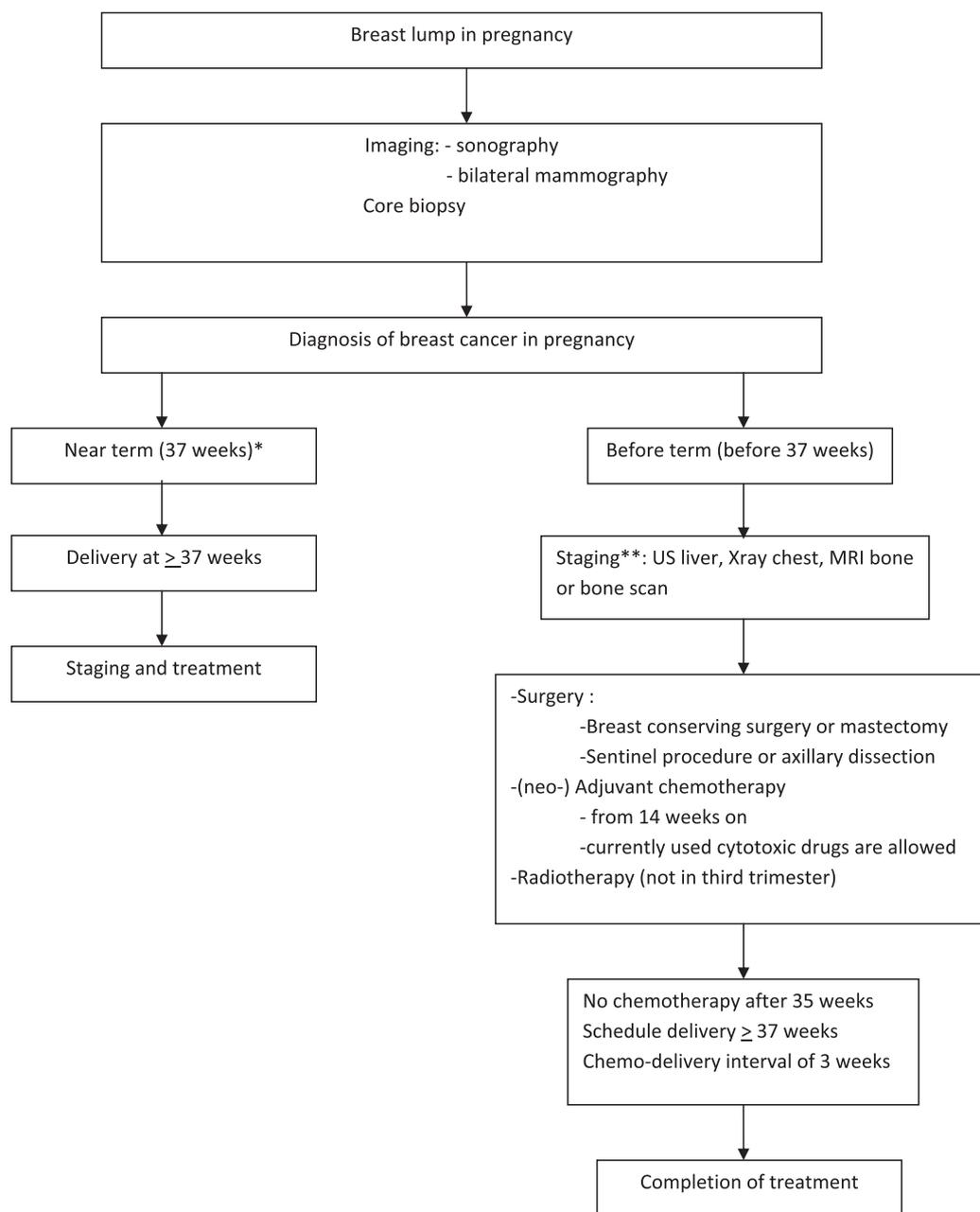
Stage of pregnancy	Therapeutic options
First trimester	– Surgery – Radiotherapy
Second trimester	– Surgery – Radiotherapy
Third trimester	– Chemotherapy – Surgery – Chemotherapy

the perioperative period.<sup>28</sup> The Shepherd Catalogue, listing agents or factors that are proven human teratogens, does not include anaesthetic agents or any drugs used routinely during the administration of anaesthesia.<sup>29</sup> Surgery and anaesthesia are safe during pregnancy if physiologic alterations are considered.<sup>28</sup> In addition, from 24 to 26 weeks of gestation onwards, intraoperative fetal heart rate monitoring can be used to detect early compromise. This permits optimisation of factors such as maternal hemodynamics, oxygenation and temperature, in order to improve the fetal condition. However, it is important that the decision to proceed to early delivery in the event of persistent fetal distress is made prior to surgery, especially between 24 and 30 weeks, since there would be little point in close monitoring if a decision not to intervene had been made. Anaesthetic agents reduce both baseline fetal heart rate and variability, so readings must be interpreted in the context of administered drugs.<sup>30</sup> In the post-operative period, tocometry is useful as post-operative analgesia may mask awareness of mild early contractions and delay tocolysis.<sup>28</sup> Adequate analgesia is important as pain has been shown to increase the risk of premature onset of labour.<sup>31</sup> Thromboprophylaxis with heparin is required because of the increased risk of thromboembolic events due to post-operative venous stasis combined with pregnancy related hypercoagulability.<sup>28</sup>

Breast surgery can safely be performed during all trimesters of pregnancy with minimal risk to the developing foetus.<sup>32</sup> Both radical modified mastectomy and breast conserving surgery with axillary or sentinel lymph node dissection can be carried out.<sup>11</sup> Breast cancer surgery should follow the same guidelines as for non-pregnant women. There are no data on reconstructive breast surgery during pregnancy. Since physiologic alterations should be taken into consideration, reconstruction – if needed – is best restricted to a prosthetic implant or it is better, to be carried out post partum.

#### 3.3.2. Radiotherapy

The dilemma is whether or not to administer radiotherapy during pregnancy to a woman who has a diagnosis of breast cancer made during the first, or early in the second trimester. If the patient is motivated to conserve her breast and it is appropriate, then there is the question of giving post-operative radiotherapy before delivery, or delaying it until later. Clearly if there is a clear indication for pre- or post-



\*a waiting policy of 2-4 weeks is allowed to attain fetal maturity

\*\*as far as this will change clinical practice

**Fig. 2 – Algorithm for the treatment of breast cancer diagnosed during pregnancy.**

operative chemotherapy, then the timing may work out such that it can be safely delayed until after delivery. Delaying radiotherapy in the management of breast cancer is likely to lead to an increased rate of local recurrence. The Panel agrees that the decision to administer radiotherapy during pregnancy should be taken after a thorough discussion of available data between the patient, her family and the multidisciplinary team, taking into account the potential benefits and risks of this treatment. Delaying radiotherapy to the post-partum period should also be considered in that detailed discussion. In patients diagnosed later on in the pregnancy, for example in the late second or third trimester, radiotherapy

could well be postponed until after delivery without detriment to the maternal outcome.

The dose to a foetus resulting from tangential breast irradiation, measured using anthropomorphic phantoms simulating the geometry of a pregnant woman, has been calculated for the first, second and third trimester of gestation.<sup>33</sup> The dose increased as the pregnancy became more advanced, because of the increased proximity of the foetus to the primary irradiation field. Table S3 gives an overview of the radiation dose to the foetus (without shielding) according to the gestational stage. With shielding a 50–75% dose reduction can be achieved.<sup>23,34</sup> These data are applicable for all the X-

ray energies from 4 to 10 MV used for breast radiotherapy. Thus, during the first and the second trimester of pregnancy, the fetal irradiation dose is considerably lower than the threshold values associated organ malformations. During the third trimester, however, the dose seems to exceed this threshold. In addition, in utero irradiation at all gestational ages may increase the risk of cancer during childhood.<sup>33</sup> A conservative estimate of the lifetime risk of radiation induced by fetal exposure to 0.01 Gy is about one in 1700 cases.<sup>23</sup> Therefore, radiotherapy is considered relatively safe only during the first and second trimester of pregnancy, if at all.

Though intraoperative radiotherapy could reduce fetal dose,<sup>35</sup> there are no available data about the efficacy of intensity modulated or intraoperative radiotherapy in pregnant women. Therefore, it cannot be recommended on a routine basis.

The recommendations are based on observed long term side effects of thousands of pregnant women (and their offspring) exposed to the atomic bomb explosions in August 1945 in Hiroshima and Nagasaki. The follow-up period of this cohort (and its offspring) is now almost 65 years. The International Commission on Radiological Protection (ICRP) coordinated and executed these studies. Based on these results, predictive models on deterministic as well as on stochastic effects have been developed and validated. Reports are published every 5 years. Results of clinical studies on the issue of pregnancy and breast cancer have also been published. But no reliable conclusions can be drawn since the total number of cases is limited and follow-up periods are too short. Moreover, most importantly these clinical studies carry the drawback of a selection bias.<sup>23</sup> The Panel encountered scarce literature data on the outcome of children whose mothers were given therapeutic irradiation during BCP. Successful radiotherapy of breast cancer during pregnancy and birth of healthy children has been reported (Table S4).<sup>17,36-41</sup> The discussion on radiotherapy and its safety during pregnancy was labourious. However, based on data on long term outcome of pregnant atomic bomb survivors and based on theoretical assumptions, the Panel accepts radiotherapy as a relatively safe treatment option during the first and second trimester of pregnancy. The Panel states that better clinical data are needed.

### 3.3.3. Chemotherapy, pharmacokinetics

Pregnancy is associated with physiological changes that influence the pharmacokinetics of cytotoxic drugs, including paclitaxel, carboplatin, doxorubicin and epirubicin.<sup>42</sup> The Panel states that although pregnancy will alter the pharmacokinetics, there are currently no studies justifying a change in dosage. Until more data are available, the current dosage of the chemotherapeutic agents should be the same for pregnant compared to that for non-pregnant women and is based on actual height and weight including established dose capping strategies. A lower pre-pregnant weight should not be used since physiologic alterations will already lower dosages.

### 3.3.4. Chemotherapy, transplacental transfer

There is fetal exposure of chemotherapy although the data are very limited in humans. Placental protein pumps including P-glycoprotein, Multidrug Resistance Proteins and Breast

Cancer Resistance Protein regulate the transfer of certain chemotherapeutic drugs such as vinblastine, doxorubicin, epirubicin and paclitaxel.<sup>43</sup> The Panel acknowledged recent data obtained in a pre-clinical study. Results in a baboon model showed that transplacental transfer of chemotherapeutics varies substantially amongst different drugs. Significant levels of platinum ( $57.5 \pm 14.2\%$  of maternal plasma levels ( $n = 7$ )) after intravenous carboplatin administration were detected in fetal plasma samples, but lower levels of doxorubicin ( $7.5 \pm 3.2\%$  ( $n = 6$ )), epirubicin ( $4.0 \pm 1.6\%$  ( $n = 8$ )), docetaxel (not detectable in fetal samples ( $n = 9$ )), paclitaxel ( $1.4 \pm 0.8\%$  ( $n = 7$ )), vinblastine ( $18.5 \pm 15.5\%$  ( $n = 9$ )) and 4-OH-cyclophosphamide ( $25.1 \pm 6.3\%$  ( $n = 3$ )) were measured.<sup>44-46</sup> Although the Panel accepts that the placenta will act as a barrier for the transfer of most chemotherapeutic drugs, reducing fetal exposure, it states that currently these data are insufficient to select a preferred chemotherapy regimen during pregnancy.

### 3.3.5. Chemotherapy for BCP

The Panel states that the decision for chemotherapy should be taken based on tumour biology and prognostic factors (tumour size and nodal involvement).<sup>47</sup> Administration of chemotherapy during the first trimester is contraindicated and should be postponed. Chemotherapy during organogenesis (2-8 weeks) is associated with miscarriage, fetal death and major malformations.<sup>48,49</sup> After organogenesis, several organs including the eyes, genitals, hematopoietic system and the central nervous system remain vulnerable to chemotherapy.<sup>50</sup> Therefore, it is recommended to wait until 14 weeks of gestation before initiating cytotoxic treatment.<sup>4</sup> During the second and third trimester, chemotherapy can be administered relatively safely.<sup>1,11,50-55</sup>

The Panel reviewed the literature on cytotoxic drugs used for breast cancer treatment. Published cases of treatment of BCP are summarised in Table S4. The most used regimens are 5-fluorouracil (F)-doxorubicin (A) or epirubicin(E)-cyclophosphamide(C), or AC. The use of C-methotrexate (M)-F, taxanes (T) and vinca alkaloids were also reported but numbers are small. Since the safety of taxanes is less documented when compared to anthracyclines, in some situations an additional cycle of anthracycline-based chemotherapy during pregnancy and completion of taxane based chemotherapy after delivery can be considered. No clear differences in terms of maternal toxicities/outcome, short or long term fetal outcome and pregnancy outcome could be attributed to different regimens. Importantly, fetal malformations did not show any trend (e.g. no excess of cardiac malformation). Chemotherapy was delivered in the vast majority of cases after the first trimester. The major cause of undesirable fetal outcome appears to be derived from premature delivery, rather than from any direct effect of the chemotherapy. Follow-up of children is reassuring, although it is short and a comprehensive and specialised assessment of the children is lacking.

Based on the literature and personal experience, the Panel considers currently used cytotoxic drugs for breast cancer relatively safe for use during pregnancy. There are insufficient data to propose one preferred regimen based on safety. Regimens that could be used in the (neo)adjuvant setting include

FEC, EC, FAC, AC and T (q1w-q3w paclitaxel/q3w docetaxel). Taxanes are non-DNA damaging agents and the transfer rate is very low.<sup>45</sup> In view of the existing data in the English literature and the experts' clinical experience, the use of taxanes during the second and third trimesters appears possible with limited risk for both the mother and the foetus. There are fetal safety data with weekly E,<sup>55</sup> but there are insufficient efficacy data as an adjuvant chemotherapy to recommend it as a standard. Since there are sufficient alternatives and given the potential fetal toxicity of M, CMF should not be used during pregnancy. Given that some standard chemotherapy regimens involve the use of single agent chemotherapy as part of a multi-agent regimen, the Panel believes that single agent Adriamycin or Epirubicin could be given as part of the treatment, acknowledging that there is a theoretical and unknown long term fetal risk for leukaemia after in utero exposure to cyclophosphamide. However, the Panel considers it important that the overall efficacy of the regimen must be maintained to avoid compromising the maternal outcome.

### 3.3.6. Long-term outcome after in utero exposure to chemotherapy

The potential for long-term sequelae from in utero exposure to cytotoxic treatment remains a major concern. The fact that the central nervous system continues to develop after the first trimester throughout gestation raises concerns regarding the long-term neuro developmental outcome.<sup>53</sup>

Aviles et al. examined 84 children exposed to chemotherapy in utero.<sup>56</sup> The observation that all the children's learning and educational performance were normal without congenital, neurologic, psychologic, cardiac, cytogenetic abnormalities or malignancies indicate even better outcome than in non treated cohorts. Hahn et al. surveyed parents/guardians by mail or telephone regarding outcomes of children exposed to chemotherapy in utero.<sup>54</sup> At the time of the survey, the age of the 40 children ranged from 2 to 157 months. Apparent problems induced by chemotherapy could not be identified. Van Calsteren et al. noted no developmental problems after a thorough cardiac and neurologic investigation in a small series of 10 children.<sup>57</sup> Echocardiographic follow-up data suggest a normal cardiac function in children following in utero exposure to cytotoxic drugs, including anthracyclines.<sup>57-59</sup> Only one report of a secondary malignancy (thyroid and neuroblastoma) after prenatal exposure to chemotherapy (cyclophosphamide) has been reported.<sup>60</sup> The twin sister however, was healthy. The Panel concludes that whilst the long term outcome of children exposed in utero to chemotherapy is poorly documented, the available evidence is reassuring with regard to outcome and chemotherapy should not be withheld for fetal reasons in the second and third trimester. The results of an international study coordinated in Leuven (Belgium) where children who were in utero exposed to chemo- or radiotherapy are neurologically and cardiologically examined are eagerly awaited.

### 3.3.7. Trastuzumab

Trastuzumab is not recommended though the fetal effect of short term use of trastuzumab needs to be further investigated. The literature includes 14 full term pregnancies that have been exposed to trastuzumab in utero.<sup>61-73</sup> Reduction

in the volume of the amniotic fluid (i.e. oligohydramnios or anhydramnios) was noted in 8/14 patients. The increased risk of oligo/anhydramnios is believed to be secondary to the effect of trastuzumab on fetal renal epithelium in which HER-2/*neu* is strongly expressed.<sup>74</sup> Another hypothesis links the effect of trastuzumab to an inhibition of vascular endothelial growth factor (VEGF), which regulates the production and re-absorption of the amniotic fluid.<sup>69</sup> The risk of oligo/anhydramnios is linked to the duration of exposure. Trastuzumab administration for brief periods (i.e. one trimester or less) may less endanger the pregnancy. However, prolonged exposure to trastuzumab should be avoided given the association with serious adverse events on both the pregnancy and foetus. Four neonatal deaths have been reported after exposure to trastuzumab in utero, secondary to respiratory and renal failure. Three more babies developed transient respiratory and/or renal failure but were successfully managed.

### 3.3.8. Other biologics

The only report on *lapatinib* describes the delivery of a healthy baby after exposure during 11 weeks to lapatinib in the first and second trimesters.<sup>75</sup> However, lapatinib is not a standard treatment for early breast cancer. In addition, given the pharmacological characteristics of lapatinib (making its massive transplacental transfer very likely) and well-known concerns regarding the use of anti-HER2 agents, its use during pregnancy cannot be recommended. There are insufficient data on *bevacizumab* but its mode of action would strongly caution against using it during pregnancy.

### 3.3.9. Tamoxifen

The Panel recommends avoiding tamoxifen during pregnancy.<sup>10</sup> Birth defects associated with use of tamoxifen include Goldenhar syndrome (oculoauriculovertebral dysplasia),<sup>76</sup> ambiguous genitalia,<sup>77</sup> and Pierre Robin sequence (triad of small mandible, cleft palate and glossoptosis).<sup>78</sup> Tamoxifen exposure throughout the whole of pregnancy has resulted in a normal outcome at 2 years follow-up in one case.<sup>79</sup> Delaying hormonal treatment will not reduce the efficacy and hormone treatment, if indicated, should be started after delivery and after completion of chemotherapy.<sup>3</sup>

### 3.3.10. Supportive therapy

Supportive treatment for chemotherapy can be given mainly according to general recommendations.<sup>80</sup> A consensus on the safe use of metoclopramide, alizapride, 5-HT antagonists, NK1 antagonists, corticosteroids, GCS-F and erythropoietins was previously established.<sup>4</sup> Regarding corticoids, the use of methylprednisolone or hydrocortisone is preferred over dexamethasone, since these glucocorticoids are extensively metabolized in the placenta, so relatively little crosses into the fetal compartment.<sup>81</sup> At the age of 2, more children receiving repeated courses of 12 mg dexamethasone for lung maturation have higher rates of attention problems and cerebral palsy.<sup>82,83</sup> Therefore, methylprednisolone or hydrocortisone should be preferred, both for the prevention of anaphylactic reaction or as an antiemetic drug. The anti-inflammatory effect of 0.75 mg dexamethasone or dexamethasone corresponds to 4 mg methylprednisolone.

Bisphosphonates have been used in a small number of patients during pregnancy without any reported negative fetal effects (Table S4). However, potential undesired effects include maternal and fetal hypocalcemia and fetal osteoclast activity inhibition. In addition, there are no indications for its use during pregnancy. Therefore, the Panel does not recommend the use of bisphosphonates during pregnancy. Safe use of G-CSF during pregnancy has been documented,<sup>84</sup> and it has also been used successfully for prevention of recurrent miscarriage.<sup>85</sup>

### 3.4. What are the important issues of prenatal care, in particular relating to the use of chemotherapy?

Prenatal care in women diagnosed with breast cancer during pregnancy should be performed as in a high-risk obstetric unit. It is important to correctly estimate the fetal risk caused by the mother's cancer treatment. Therefore, before starting staging examinations and treatment, an ultrasound of the foetus should be performed to ensure that the foetus has undergone normal development and growth to date.<sup>3</sup> Before every cycle of cytotoxic treatment, an evaluation of fetal morphology, growth and wellbeing must be carried out by ultrasound screening, if indicated with Doppler including the measurement of peak systolic velocity of the middle cerebral artery.<sup>86</sup> In case of abnormal findings a more intense fetal monitoring or even (preterm) delivery may be required. After treatment, it is important to consider fetal wellbeing and counsel patients to be alert when contractions occur, since an increased incidence in preterm contractions was reported after cytotoxic treatment during pregnancy.<sup>1</sup> The timing of delivery should be balanced according to the oncological treatment schedule and the maturation of the foetus. As in non cancer patients, term delivery ( $\geq 37$  weeks) should be aimed for.<sup>1</sup> Early induction results in prematurity and low birth weight that have been identified as contributing factors in the cognitive and emotional development of children. In the event that preterm delivery is inevitable, fetal lung maturation should be considered and managed according to local policy. The mode of delivery is determined based on obstetrical indication. If continuation of therapy is required postpartum, a vaginal delivery is recommended since this is associated with a lower risk of therapy delay due to lower maternal morbidity.<sup>87</sup> To allow the bone marrow to recover and to minimise the risk of maternal and fetal neutropaenia, delivery should be planned 3 weeks after the last dose of anthracycline-based chemotherapy.<sup>3</sup> Timing of delivery also needs to be coordinated according to the nadir of blood counts from the last chemotherapy cycle. Chemotherapy should not be administered after 35 weeks since spontaneous labour becomes more likely. This policy minimises the risk of neutropaenia at the time of delivery. Furthermore, neonates, especially preterm babies, have limited capacity to metabolise and eliminate drugs due to liver and renal immaturity. The delay of delivery after chemotherapy will allow fetal drug excretion via the placenta.<sup>88</sup> Chemotherapy can be restarted when needed after delivery. An interval of 1 week after an uncomplicated caesarean section is needed. Although placental metastases in breast cancer are rare, the placenta should be analysed

histopathologically after delivery.<sup>89,90</sup> In the absence of safety data, breastfeeding shortly after chemotherapy is not recommended. Primary inhibition of milk production is needed because especially lipophilic agents as taxanes can accumulate in the milk.

## 4. Summary

Efficient treatment of breast cancer during pregnancy is possible. The Panel recommends a plan of care that integrates the physical and emotional well being of the mother with the health of the foetus. The different diagnostic, staging and treatment options should be discussed by a multidisciplinary team with sufficient expertise to ensure optimal treatment and support of the patient. Referral to an experienced multidisciplinary team, including neonatal, perinatal, obstetrical, breast surgical and oncological care is recommended. The treatment of BCP should adhere as closely as possible to standardised protocols for non-pregnant patients. Breast surgery can safely be performed during all trimesters of pregnancy and the type of surgery is independent from the pregnant state. Radiation therapy of the breast can be considered during the first and second trimester of pregnancy, taking care of the fetal threshold doses. Chemotherapy, using the same protocols as for non-pregnant women, can be administered during the second and third trimester. Although preliminary data indicate that the serum levels of cytotoxic drugs are lower during pregnancy, standard dosages based on actual height and weight should be used. Trastuzumab and tamoxifen should be avoided during pregnancy. If possible, delivery should not be induced before the 37th week. Patients that are diagnosed with cancer during pregnancy should be registered and included in studies that will increase the knowledge. Such initiatives exist within the German Breast Group, within an international study on cancer in pregnancy (<http://www.cancerinpregnancy.org>) and within the European Society of Gynecological Oncology, where a task force on cancer in pregnancy gathers local and national initiatives.

## Conflict of interest statement

None declared.

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## Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at [doi:10.1016/j.ejca.2010.09.010](https://doi.org/10.1016/j.ejca.2010.09.010).

## REFERENCES

1. 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**(4):683-9.
2. du Bois A, Meerpohl HG, Gerner K, et al. Effect of pregnancy on the incidence and course of malignant diseases. *Geburtshilfe Frauenheilkd* 1993;**53**(9):619-24.
3. Loibl S, von Minckwitz G, Gwyn K, et al. Breast carcinoma during pregnancy. International recommendations from an expert meeting. *Cancer* 2006;**106**(2):237-46.
4. 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-S12.
5. Garcia-Manero M, Royo MP, Espinos J, et al. Pregnancy associated breast cancer. *Eur J Surg Oncol* 2009;**35**(2):215-8.
6. Woo JC, Yu T, Hurd TC. Breast cancer in pregnancy: a literature review. *Arch Surg* 2003;**138**(1):91-8.
7. Nettleton J, Long J, Kuban D, et al. Breast cancer during pregnancy: quantifying the risk of treatment delay. *Obstet Gynecol* 1996;**87**(3):414-8.
8. Loman N, Johannsson O, Kristoffersson U, et al. Family history of breast and ovarian cancers and BRCA1 and BRCA2 mutations in a population-based series of early-onset breast cancer. *J Natl Cancer Inst* 2001;**93**(16):1215-23.
9. Samphao S, Wheeler AJ, Rafferty E, et al. Diagnosis of breast cancer in women age 40 and younger: delays in diagnosis result from underuse of genetic testing and breast imaging. *Am J Surg* 2009;**198**(4):538-43.
10. Eedarapalli P, Jain S. Breast cancer in pregnancy. *J Obstet Gynaecol* 2006;**26**(1):1-4.
11. Navrozoglou I, Vrekoussis T, Kontostolis E, et al. Breast cancer during pregnancy: a mini-review. *Eur J Surg Oncol* 2008;**34**(8):837-43.
12. Shellock FG, Kanal E. Policies, guidelines, and recommendations for MR imaging safety and patient management. SMRI Safety Committee. *J Magn Reson Imaging* 1991;**1**(1):97-101.
13. Oto A, Ernst R, Jesse MK, et al. Magnetic resonance imaging of the chest, abdomen, and pelvis in the evaluation of pregnant patients with neoplasms. *Am J Perinatol* 2007;**24**(4):243-50.
14. Bellin MF, Webb JA, Van Der Molen AJ, et al. Safety of MR liver specific contrast media. *Eur Radiol* 2005;**15**(8):1607-14.
15. Oyama T, Koibuchi Y, McKee G. Core needle biopsy (CNB) as a diagnostic method for breast lesions: comparison with fine needle aspiration cytology (FNA). *Breast Cancer* 2004;**11**(4):339-42.
16. Parente JT, Amsel M, Lerner R, et al. Breast cancer associated with pregnancy. *Obstet Gynecol* 1988;**71**(6 Pt 1):861-4.
17. King RM, Welch JS, Martin Jr JK, et al. Carcinoma of the breast associated with pregnancy. *Surg Gynecol Obstet* 1985;**160**(3):228-32.
18. Tobon H, Horowitz LF. Breast cancer during pregnancy. *Breast Dis* 1993;**6**:127-34.
19. Cardonick E, Dougherty R, Grana G, et al. Breast cancer during pregnancy: maternal and fetal outcomes. *Cancer J* 2010;**16**(1):76-82.
20. Stensheim H, Moller B, van Dijk T, et al. Cause-specific survival for women diagnosed with cancer during pregnancy or lactation: a registry-based cohort study. *J Clin Oncol* 2009;**27**(1):45-51.
21. 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**(5):461-7.
22. Hall EJ. Scientific view of low-level radiation risks. *Radiographics* 1991;**11**(3):509-18.
23. Kal HB, Struikmans H. Radiotherapy during pregnancy: fact and fiction. *Lancet Oncol* 2005;**6**(5):328-33.
24. Gentilini O, Cremonesi M, Trifiro G, et al. Safety of sentinel node biopsy in pregnant patients with breast cancer. *Ann Oncol* 2004;**15**(9):1348-51.
25. 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**(1):78-83.
26. Khera SY, Kiluk JV, Hasson DM, et al. Pregnancy-associated breast cancer patients can safely undergo lymphatic mapping. *Breast J* 2008;**14**(3):250-4.
27. Jones AL. Management of pregnancy-associated breast cancer. *Breast* 2006;**15**(Suppl 2):S47-52.
28. Ni Mhuireachtaigh R, O'Gorman DA. Anesthesia in pregnant patients for nonobstetric surgery. *J Clin Anesth* 2006;**18**(1):60-6.
29. Crawford JS, Lewis M. Nitrous oxide in early human pregnancy. *Anaesthesia* 1986;**41**(9):900-5.
30. Cheek T, Baird E. Anesthesia for nonobstetric surgery: maternal and fetal considerations. *Clin Obstet Gynecol* 2009;**52**(4):535-45.
31. Sanson BJ, Lensing AW, Prins MH, et al. Safety of low-molecular-weight heparin in pregnancy: a systematic review. *Thromb Haemost* 1999;**81**(5):668-72.
32. Duncan PG, Pope WD, Cohen MM, et al. Fetal risk of anesthesia and surgery during pregnancy. *Anesthesiology* 1986;**64**(6):790-4.
33. Mazonakis M, Varveris H, Damilakis J, et al. Radiation dose to conceptus resulting from tangential breast irradiation. *Int J Radiat Oncol Biol Phys* 2003;**55**(2):386-91.
34. 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**(6):581-9.
35. Galimberti V, Ciocca M, Leonardi MC, et al. Is electron beam intraoperative radiotherapy (ELIOT) safe in pregnant women with early breast cancer? In vivo dosimetry to assess fetal dose. *Ann Surg Oncol* 2009;**16**(1):100-5.
36. 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**(3):257-64.
37. Ngu SL, Duval P, Collins C. Foetal radiation dose in radiotherapy for breast cancer. *Australas Radiol* 1992;**36**(4):321-2.
38. Antypas C, Sandilos P, Kouvaris J, et al. Fetal dose evaluation during breast cancer radiotherapy. *Int J Radiat Oncol Biol Phys* 1998;**40**(4):995-9.
39. Luis SA, Christie DR, Kaminski A, et al. Pregnancy and radiotherapy: management options for minimising risk, case series and comprehensive literature review. *J Med Imaging Radiat Oncol* 2009;**53**(6):559-68.
40. Kouvaris JR, Antypas CE, Sandilos PH, et al. Postoperative tailored radiotherapy for locally advanced breast carcinoma during pregnancy: a therapeutic dilemma. *Am J Obstet Gynecol* 2000;**183**(2):498-9.
41. Cohen Y, Thatcher M, Robinson E. Radiotherapy in pregnancy. A case report with estimation of the dose to the fetus. *Radiol Clin Biol* 1973;**42**(1):34-9.
42. 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.
43. Syme MR, Paxton JW, Keelan JA. Drug transfer and metabolism by the human placenta. *Clin Pharmacokinet* 2004;**43**(8):487-514.

44. Van Calsteren K, Verbesselt R, Van Bree R, et al. Substantial variation in transplacental transfer of chemotherapeutic agents in a mouse model. *Reprod Sci*, in press [PMID: 20826505].
45. Van Calsteren K, Verbesselt R, Beijnen J, et al. Transplacental transfer of paclitaxel, docetaxel, carboplatin and trastuzumab in a baboon model. *Int J Gynecol Cancer* 2010, in press.
46. Van Calsteren K, Verbesselt R, Beijnen J, et al. Transplacental transfer of anthracyclines, vinblastine and 4-hydroxycyclophosphamide in a baboon model. *Gynecol Oncol* 2010. doi:10.1016/j.ygyno.2010.08.019.
47. Goldhirsch A, Ingle JN, Gelber RD, et al. Thresholds for therapies: highlights of the St Gallen International Expert Consensus on the primary therapy of early breast cancer 2009. *Ann Oncol* 2009;20(8):1319–29.
48. Doll DC, Ringenberg QS, Yarbrow JW. Antineoplastic agents and pregnancy. *Semin Oncol* 1989;16(5):337–46.
49. Zemlickis D, Lishner M, Degendorfer P, et al. Fetal outcome after in utero exposure to cancer chemotherapy. *Arch Intern Med* 1992;152(3):573–6.
50. Cardonick E, Iacobucci A. Use of chemotherapy during human pregnancy. *Lancet Oncol* 2004;5(5):283–91.
51. Ring AE, Smith IE, Ellis PA. Breast cancer and pregnancy. *Ann Oncol* 2005;16(12):1855–60.
52. Mir O, Berveiller P, Ropert S, et al. Emerging therapeutic options for breast cancer chemotherapy during pregnancy. *Ann Oncol* 2008;19(4):607–13.
53. Pereg D, Koren G, Lishner M. Cancer in pregnancy: gaps, challenges and solutions. *Cancer Treat Rev* 2008;34(4):302–12.
54. 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(6):1219–26.
55. Peccatori FA, Azim Jr HA, Scarfone G, et al. Weekly epirubicin in the treatment of gestational breast cancer (GBC). *Breast Cancer Res Treat* 2009;115(3):591–4.
56. Aviles A, Neri N. Hematological malignancies and pregnancy: a final report of 84 children who received chemotherapy in utero. *Clin Lymphoma* 2001;2(3):173–7.
57. 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(12):e16–7.
58. Meyer-Wittkopf M, Barth H, Emons G, et al. Fetal cardiac effects of doxorubicin therapy for carcinoma of the breast during pregnancy: case report and review of the literature. *Ultrasound Obstet Gynecol* 2001;18(1):62–6.
59. Aviles A, Neri N, Nambo MJ. Long-term evaluation of cardiac function in children who received anthracyclines during pregnancy. *Ann Oncol* 2006;17(2):286–8.
60. Zemlickis D, Lishner M, Erlich R, et al. Teratogenicity and carcinogenicity in a twin exposed in utero to cyclophosphamide. *Teratog Carcinog Mutagen* 1993;13(3):139–43.
61. Watson WJ. Herceptin (trastuzumab) therapy during pregnancy: association with reversible anhydramnios. *Obstet Gynecol* 2005;105(3):642–3.
62. Fanale MA, Uyei AR, Theriault RL, et al. Treatment of metastatic breast cancer with trastuzumab and vinorelbine during pregnancy. *Clin Breast Cancer* 2005;6(4):354–6.
63. Waterston AM, Graham J. Effect of adjuvant trastuzumab on pregnancy. *J Clin Oncol* 2006;24(2):321–2.
64. Bader AA, Schlembach D, Tamussino KF, et al. Anhydramnios associated with administration of trastuzumab and paclitaxel for metastatic breast cancer during pregnancy. *Lancet Oncol* 2007;8(1):79–81.
65. Sekar R, Stone PR. Trastuzumab use for metastatic breast cancer in pregnancy. *Obstet Gynecol* 2007;110(2 Pt 2):507–10.
66. Shrim A, Garcia-Bournissen F, Maxwell C, et al. Favorable pregnancy outcome following trastuzumab (herceptin) use during pregnancy – case report and updated literature review. *Reprod Toxicol* 2007;23(4):611–3.
67. Witzel ID, Muller V, Harps E, et al. Trastuzumab in pregnancy associated with poor fetal outcome. *Ann Oncol* 2008;19(1):191–2.
68. Berveiller P, Mir O, Sauvanet E, et al. Ectopic pregnancy in a breast cancer patient receiving trastuzumab. *Reprod Toxicol* 2008;25(2):286–8.
69. Pant S, Landon MB, Blumenfeld M, et al. Treatment of breast cancer with trastuzumab during pregnancy. *J Clin Oncol* 2008;26(9):1567–9.
70. Beale JM, Tuohy J, McDowell SJ. Herceptin (trastuzumab) therapy in a twin pregnancy with associated oligohydramnios. *Am J Obstet Gynecol* 2009;201(1):e13–4.
71. Warrach Q, Smith N. Herceptin therapy in pregnancy: continuation of pregnancy in the presence of anhydramnios. *J Obstet Gynaecol* 2009;29(2):147–8.
72. Azim Jr HA, Peccatori FA, Liptrott SJ, et al. Breast cancer and pregnancy: how safe is trastuzumab? *Nat Rev Clin Oncol* 2009;6(6):367–70.
73. Weber-Schoendorfer C, Schaefer C. Trastuzumab exposure during pregnancy. *Reprod Toxicol* 2008;25:390–1.
74. 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(7):953–62.
75. Kelly H, Graham M, Humes E, et al. Delivery of a healthy baby after first-trimester maternal exposure to lapatinib. *Clin Breast Cancer* 2006;7(4):339–41.
76. Cullins SL, Pridjian G, Sutherland CM. Goldenhar's syndrome associated with tamoxifen given to the mother during gestation. *JAMA* 1994;271(24):1905–6.
77. Tewari K, Bonebrake RG, Asrat T, et al. Ambiguous genitalia in infant exposed to tamoxifen in utero. *Lancet* 1997;350(9072):183.
78. Berger JC, Clericuzio CL. Pierre Robin sequence associated with first trimester fetal tamoxifen exposure. *Am J Med Genet A* 2008;146A(16):2141–4.
79. 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(3):405–8.
80. Gralla RJ, Osoba D, Kris MG, et al. Recommendations for the use of antiemetics: evidence-based, clinical practice guidelines. American Society of Clinical Oncology. *J Clin Oncol* 1999;17(9):2971–94.
81. Blanford AT, Murphy BE. In vitro metabolism of prednisolone, dexamethasone, betamethasone, and cortisol by the human placenta. *Am J Obstet Gynecol* 1977;127(3):264–7.
82. Crowther CA, Doyle LW, Haslam RR, et al. Outcomes at 2 years of age after repeat doses of antenatal corticosteroids. *New Engl J Med* 2007;357(12):1179–89.
83. Wapner RJ, Sorokin Y, Mele L, et al. Long-term outcomes after repeat doses of antenatal corticosteroids. *New Engl J Med* 2007;357(12):1190–8.
84. 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(2):82–93.
85. Scarpellini F, Sbracia M. Use of granulocyte colony-stimulating factor for the treatment of unexplained recurrent miscarriage: a randomised controlled trial. *Human Reprod* 2009;24(11):2703–8.
86. Delle CL, Buck G, Grab D, et al. Prediction of fetal anemia with Doppler measurement of the middle cerebral artery peak systolic velocity in pregnancies complicated by maternal blood group alloimmunization or parvovirus B19 infection. *Ultrasound Obstet Gynecol* 2001;18(3):232–6.

87. Lydon-Rochelle M, Holt VL, Martin DP, et al. Association between method of delivery and maternal rehospitalization. *JAMA* 2000;**283**(18):2411-6.
88. Sorosky JI, Sood AK, Buekers TE. The use of chemotherapeutic agents during pregnancy. *Obstet Gynecol Clin North Am* 1997;**24**(3):591-9.
89. Alexander A, Samlowski WE, Grossman D, et al. Metastatic melanoma in pregnancy: risk of transplacental metastases in the infant. *J Clin Oncol* 2003;**21**(11):2179-86.
90. Dunn Jr JS, Anderson CD, Brost BC. Breast carcinoma metastatic to the placenta. *Obstet Gynecol* 1999;**94**(5 Pt 2): 846.