Chemotherapy for breast cancer in pregnancy: evidence and guidance for oncologists

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***Abstract*:** It has been estimated that up to 3.8% of breast cancers may be diagnosed in women who are pregnant, with an estimated 1 in 3000–3500 deliveries occurring in women with breast cancer. Owing to the lack of large randomized trials available to guide our clinical practice, our decisions regarding adjuvant systemic management are based on retrospective analyses, case reports and a small number of prospective studies. A tailored approach to treatment is required with careful consideration given at all stages to the needs of the mother and risks to the foetus. Management is critically influenced by the stage of pregnancy, especially the first trimester. Anthracycline-based chemotherapy may be administered during the second and third trimesters, with apparently few short-term implications. Limited data shows the taxanes may also be given with few adverse events at these stages. Weekly fractionation regimens may allow closer monitoring of pregnancy with prompt termination of agents, if necessary. Data concerning the long-term risks of systemic anticancer treatment are limited. All stages of patient management should be discussed within a multidisciplinary team and a clear consensus of treatment options communicated to the mother. Delaying chemotherapy until after delivery may be reasonable in some cases, but where the delay is likely to be prolonged, a decision must be made on the basis of risks *versus* benefits.

***Keywords*:** breast cancer, chemotherapy, pregnancy

Introduction

It has been estimated that up to 3.8% of breast cancers may be diagnosed in women who are pregnant [Wallack *et al.* 1983], with an estimated 1 in 3000–3500 deliveries occurring in women with breast cancer [Smith *et al.* 2001; Anderson, 1979; White, 1955]. This incidence is expected to increase further with the rising trend of delaying childbirth to later in life, and the increasing number of premenopausal women diagnosed with breast cancer [Ranstam *et al.* 1990; Ventura, 1989].

The management of pregnant women with breast cancer presents a considerable challenge, mandating changes in approach to the diagnosis and staging of the disease and the planning of locoregional and systemic therapies. Throughout the diagnostic and treatment pathway, there is a need to optimize the treatment of the mother, but at the same time to minimize the risks to the foetus. From first presentation, diagnosis is complicated by the physiological changes in the breast and need to avoid ionizing radiation, these factors together with the need for general anaesthesia also complicate locoregional treatment. These issues have been discussed in previous publications [Loibl *et al.* 2006; Ring *et al.* 2005a] and they are not the focus of this review, which concentrates on adjuvant systemic therapy.

Owing to the lack of large randomized trials available to guide our clinical practice, our decisions regarding adjuvant systemic management are based on retrospective analyses, case reports and a small number of prospective studies. In this review we describe the available data and provide some guidance as to appropriate strategies.

Clinical and pathological features of pregnancy-associated breast cancer

Several series have shown that the median maternal age at the time of diagnosis of breast cancer during pregnancy is 33–34 years, and that the median gestational age at diagnosis is 17–25 weeks [Ring *et al.* 2005b; Middleton *et al.* 2003; Berry *et al.* 1999; Giacalone *et al.* 1999].

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The majority of tumours in women presenting with breast cancer during pregnancy are high-grade invasive ductal carcinomas displaying lymphovascular invasion. These are often large at time of diagnosis, may be associated with pathological lymph node involvement, and overall most series suggest they are more advanced than tumours seen in matched nonpregnant patients [Ishida *et al.* 1992; Zemlickis *et al.* 1992a]. The incidence of inflammatory tumours lies between 1.5% and 4% [Clark and Chua, 1989].

Approximately 60–80% of breast cancers diagnosed in pregnant women may be oestrogen receptor (ER) negative [Aziz *et al.* 2003; Bonnier *et al.* 1997; Ishida *et al.* 1992], and between 28% and 58% have been reported to be human epidermal growth factor receptor (EGFR) 2 (HER2) positive [Aziz *et al.* 2003; Middleton *et al.* 2003; Elledge *et al.* 1993]. One small study has also shown EGFR to be more commonly expressed in pregnancy-associated breast tumours than in those not diagnosed during pregnancy (33% *versus* 19%, $p = 0.005$) [Aziz *et al.* 2003]. Therefore, breast cancers presenting in pregnant women often present with adverse prognostic features. However, it is not clear whether these high rates of adverse prognostic features are a reflection of pregnancy-associated breast cancer, or simply reflect the patient age group being studied. Irrespective of this, the young age of the patient population and the high rates of adverse pathological features described, means that there is often an indication to consider adjuvant chemotherapy in pregnant women who have breast cancer.

Cytotoxic chemotherapy

There are two key factors when considering chemotherapy in pregnant women: changes in maternal physiology and the stage of foetal development.

Maternal physiology

In the pregnant woman there are significant alterations in circulating blood volume, hepatic metabolism, renal plasma flow, all of which can affect the clearance of drugs [Redmond, 1985]. Decreased plasma albumin and increases in other proteins owing to high circulating oestrogen levels will alter drug–protein binding [Wiebe and Sipila, 1994]. Therefore, it becomes difficult to be certain that the optimal dose of chemotherapy is still being delivered to the sites of disease. Elimination of agents may also be delayed due to the presence of amniotic fluid acting as a pharmacological third space. These effects may increase the chances of maternal toxicity, and may have profound effects on the developing foetus.

Foetal development

The first stage of foetal development is implantation, which usually occurs within 2 weeks following conception. Organogenesis then takes place over the following 8 weeks of foetal development. Physical or pharmacological insults during this period are believed to precipitate major malformations or foetal loss [Doll *et al.* 1989]. The effects of cytotoxic chemotherapy on nucleic acid synthesis and microtubule function, and the rapid rate of cell division occurring in the foetus during this period, mean that it is likely to be particularly susceptible to the effects of chemotherapy. At the end of this period, all of the major organ systems have been formed, despite the foetus only being around 3 cm. The extent of drug transfer across the placenta depends on the physical and chemical properties of the agent [Ring *et al.* 2005a]; however, the presence of P-glycoprotein expressed in the human placenta, may reduce foetal exposure to several antineoplastic agents [Smit *et al.* 1999]. In general, insults during this first trimester can result in major malformations [Nicholson, 1968]; however, once organogenesis is complete, such malformations are unlikely. Even so, chemotherapy after the first trimester is not without risk: as the foetus still needs to grow and mature, and some organ systems, in particular the central nervous system and gonads develop later in foetal life.

Clinical studies in breast cancer

First trimester

A number of patients have been exposed to chemotherapy during the first trimester, the majority of whom have undergone spontaneous abortion or foetal malformation [Ring *et al.* 2005b; Giacalone *et al.* 1999]. For example, an unintentional pregnancy was diagnosed on week 16 during a course of 5-fluorouracil, doxorubicin and cyclophosphamide (FAC) chemotherapy [Paskulin *et al.* 2005]. The newborn had ventriculomegaly, bicuspid aortic valve, high arched palate and syndactyly, possible related to the administration of chemotherapy during the first trimester. Overall, antimetabolites, such as methotrexate, and alkylating agents, such as cyclophosphamide, are more likely to be associated

with miscarriage and malformations [Bawle *et al.* 1998; Glantz, 1994; Zemlickis *et al.* 1992b; Schapira and Chudley, 1984]. In contrast the anthracyclines and vinca-alkaloids have not been associated with birth defects [Turchi and Villasis, 1988; Gililland and Weinstein, 1983]. When live births do occur, historical studies suggest that foetal malformation rates are between 10% and 20% [Woo *et al.* 2003; Ebert *et al.* 1997; Zemlickis *et al.* 1992b; Doll *et al.* 1989], however this risk is thought to increase when combination therapy is used, and when chemotherapy is given in conjunction with radiotherapy [Espié and Cuvier, 1998]. As a result, chemotherapy is generally avoided during the first trimester.

Second and third trimester

Beyond the first trimester, as organogenesis is complete, the use of cytotoxic chemotherapy has been more widespread and does not appear to increase the risk of malformations. In fact, the rate of congenital malformations has been reported as less than 3% [Woo *et al.* 2003; Ebert *et al.* 1997; Doll *et al.* 1989], which is similar to the baseline population risk of major malformations [Kalter and Warkany, 1983].

Regarding breast cancer, the regimens for which the most information is available are the anthracycline-based regimens, with most reports noting the absence of any congenital anomalies, although these have all been small series or case reports [Halaska *et al.* 2009; García-Manero *et al.* 2009; Morris *et al.* 2009; De Carolis *et al.* 2006].

A number of case series of pregnant women with breast cancer have now reported; of these, 5 series have included 20 or more patients (Table 1).

In a recent publication, 104 women diagnosed with breast cancer during pregnancy were reported to the Cancer and Pregnancy Registry between 1996 and 2009, and received chemotherapy during pregnancy. Cardonick and colleagues published the maternal and foetal outcomes of these prospectively and retrospectively enrolled patients [Cardonick *et al.* 2010]. Mean maternal age at diagnosis was 34.8 years (range 23–47 years), with a mean gestational age at diagnosis of 13.2 weeks. Invasive ductal carcinoma was the most common subtype, with 58% expressing ER negative, and 75% HER2 negative tumours. Lymph node status was positive in 53% of patients. All but one patient (vinorelbine single agent) received anthracycline-based treatment, with 11 patients receiving additional taxane therapy and none receiving trastuzumab. The mean gestational age at delivery was 35.8 ± 1.9 weeks and the birth weight was 2836 ± 1075 g. Eight women delivered infants with birth weight less than 10% for gestational age. One of these children developed thrombocytopenia and a rash soon after birth, with maternal platelet antibodies excluded. Diagnosis of a systemic autoimmune disorder was made, resulting in death at 13 months. The mother had received two courses of adriamycin plus cyclophosphamide (AC) chemotherapy during pregnancy up to 26 days predelivery. Birth defects were reported in four (3.8%) newborns and included pyloric stenosis, asymptomatic pulmonary artery fistula, holoprosencephalopathy, and talipes and a haemangioma in the same child. Ultimately there was no increased rate of growth restriction at birth or congenital anomalies compared with population standards. Of note, pregnant women experienced more nausea and paraesthesias while receiving chemotherapy during pregnancy than they experienced postpartum with the same agents. Also breast feeding was only successful in 55% of patients, with 45% reporting little milk production. In two children, long-term follow up (mean follow-up age of 41.8 ± 32 months) has shown gastro-esophageal reflux, pneumonia, corneal abrasion, IgA deficiency, otitis media and speech delay.

In the prospectively designed series from the M.D. Anderson Cancer Centre [Hahn *et al.* 2006], 57 women with primary or recurrent breast cancer were treated with doxorubicin 50 mg/m^2 as a continuous infusion over 72 hours, cyclophosphamide 500 mg/m^2 on day 1 only and bolus 5-fluorouracil 500 mg/m^2 on days 1 and 4, all administered every 3–4 weeks. The majority of the patients presented with invasive ductal carcinoma (85%), poorly differentiated (82%), HER2-negative (71%) and ER-negative (69%) tumours. Of those who underwent surgery before receiving chemotherapy, almost 70% had positive lymph nodes at diagnosis. Thirty two women were treated in the adjuvant setting and 25 received neoadjuvant treatment. The median gestational age at chemotherapy initiation was 23 weeks (range 11–34 weeks). The median number of cycles given whilst pregnant was four and the median gestational age at delivery was 37 weeks (range 29–42 weeks). No stillbirths, miscarriages or perinatal deaths occurred in the cohort of

Table 1. Case series of women ($n > 20$) with breast cancer receiving chemotherapy during pregnancy.

Study	Number of patients	Regimen	Gestational age at starting chemotherapy	Gestational age at delivery	Birth weight	Congenital anomalies
Cardonick *et al.* [2010]	130	AC (69%), FAC, FEC, A single agent, V single agent taxane also given in 11 cases	Mean 20.4 ± 5.4 wks	Mean 35.8 ± 1.9 wks	Mean 2836 ± 1075 g	Four cases (3.8%): – pyloric stenosis – asymptomatic pulmonary artery fistula – holoprosencephalopathy – talipes and haemangioma
Hahn *et al.* [2006]	57	FAC	Median 23 wks (range 11–34)	Median 37 wks (range 29–42)	Median 2890 g (range 1389–3977)	Three cases (5.3%): – Down's syndrome – ureteral reflux – club foot
Peccatori *et al.* [2009]	20	Weekly epirubicin 35 mg/m^2	Median 19 wks (range, 16–30)	Median 35 wks (range, 28–40)	Not published	One case (5%): – polycystic kidney
Azim *et al.* [2008]	26	Anthracycline-based (E = 23, A = 3)	Second trimester in all patients	Median 35 wks (28–40)	Not published	One case (3.8%): – polycystic kidney
Ring *et al.* [2005b]	28	AC (N = 11), EC (N = 5), CMF (N = 12)	Median 20 wks (range 15–33)	Median 37 wks (range, 30–40)	Median 3000 g (range 1400–3500)	Nil

A, adriamycin; C, cyclophosphamide; F, 5-flurouracil; E, epirubicin; V, vinorelbine; M, methotrexate; wks, weeks.

children who received FAC chemotherapy during their second and/or third trimesters, and only the child born at 29 weeks secondary to maternal pre-eclampsia weighed less than 2000 g. Only six children weighed less than 2500 g at birth, with the median weight being 2890 g (range 1389–3977 g). Ten percent of neonates ($n = 4$) had breathing difficulties requiring ventilation, one had a subarachnoid haemorrhage, one had Down's syndrome and two had congenital anomalies (club foot; congenital bilateral ureteral reflux), however these figures were similar to reported norms for the general population [Agrawal *et al.* 2003; Wen *et al.* 2001]. All but the child with Down's syndrome were thought to have normal development. At a median follow-up duration of 38.5 months (range 1.0–189.0 months), 70% ($n = 40$) of women were alive and free of disease. Of the 13 patients confirmed to have died, all died of metastatic breast cancer except one who died from a pulmonary embolism postcaesarean section.

The European Institute of Oncology in Milan reported a retrospective series where 20 women with locally advanced or metastatic breast cancer or with high risk of recurrence postsurgery were treated with weekly epirubicin (35 mg/m^2) from the second trimester onwards [Peccatori *et al.* 2009]. Weekly epirubicin is not a standard regimen in the adjuvant treatment of breast cancer; however, the authors hypothesized that this regimen would allow lower peak plasma concentration of the drug, thus lowering the risk of maternal myelotoxicity and possible placental transfer of the drug. Median gestational age at breast cancer diagnosis was 12 weeks (range 5–10 weeks), while median gestational age at chemotherapy administration was 19 weeks (range 16–30 weeks). Fifty percent of patients had ER-negative disease, and 80% had HER2-negative tumours. Weekly epirubicin was well tolerated with no grade III–IV toxicities reported and no congenital anomalies occurred with the exception of one child with polycystic kidneys.

Median gestational age at delivery was 35 weeks (range 28–40 weeks). The development of all children was normal at a median follow up of 2 years. In pregnant women, epirubicin has a shorter terminal half life than doxorubicin because of glucuronidation [Kushari and Mukherjea, 1980]. Epirubicin also has a better therapeutic index and fewer systemic and cardiac toxic effects in nonpregnant women [Bonadonna *et al.* 1993]. The authors therefore suggest that the weekly schedule may improve early identification of any pregnancy-related adverse events and reassure patients, whilst maintaining efficacy.

Azim and colleagues reported the effects of anthracycline-based regimens on the course and outcome of pregnancy in 26 patients with pregnancy-associated breast cancer [Azim *et al.* 2008]. Sixteen patients (61%) received adjuvant treatment, nine (35%) neoadjuvant and one (4%) was treated in the metastatic setting. Chemotherapy was delivered during the second trimester with a median number of four cycles (range 2–5). No pre-eclampsia or intrauterine growth restriction was observed, and median gestational age at delivery was 35 weeks (range 28–40 weeks) with two preterm deliveries. One newborn had polycystic kidneys, but all children had normal development at a median follow up of 27 months (range 0–84 months), however the authors do acknowledge that this follow-up period may be too short to exclude the possibility of cardiotoxicity.

In a London teaching hospital-based retrospective series, 27 children were exposed to chemotherapy in the second or third trimester, one in the first trimester, none of whom had congenital malformations [Ring *et al.* 2005b]. Sixteen patients received anthracycline-based treatment, with 12 receiving cyclophosphamide, methotrexate and fluorouracil (CMF). Three episodes of maternal febrile neutropenia were recorded but responded to antibiotics. The only other grade III or IV toxicities recorded were lethargy and alopecia. The median gestational age at delivery was 37 weeks (range 30–40 weeks). In one case premature delivery occurred as a result of spontaneous onset of preterm labour; however, in eight cases early delivery was planned in order to optimize the timing of delivery relative to chemotherapy or further required treatment. Birth weights were only available in 17 babies, with a median weight of 3.0 kg (1.4–3.5 kg), however none were lower than the 10th percentile for gestational age. Although there were no recorded foetal abnormalities, five of the newborns needed to be transferred to neonatal high-dependency units, with two experiencing respiratory distress. There was no evidence of neonatal myelosuppression, reflecting the mean interval of 30 days between delivery and the last chemotherapy cycle. At a median follow-up period of 40.5 months (range 7–159 months), the combined survival rate for women with stage I to IIIB breast cancer was 67%, and the disease-free survival rate was 63%. Two of the women with stage IV disease died within 3 years of diagnosis.

The young age of the patients and the adverse prognostic features frequently exhibited by pregnancy-associated breast cancers means that if such women were not pregnant, taxanes would be routinely considered as adjuvant or neoadjuvant therapy. However, paclitaxel and docetaxel have been shown to be toxic to the foetus in animal studies during organogenesis. Nonetheless, several case reports describe their use in the second and third trimesters, either as single agents or in combination, with no indication of greater risk or specific complications [García-Manero M. *et al.* 2009; Morris *et al.* 2009; Lycette *et al.* 2006; Nieto *et al.* 2006; Potluri *et al.* 2006; Gonzalez-Angulo *et al.* 2004; Gadducci *et al.* 2003; De Santis *et al.* 2000]. In a systematic review, Mir and colleagues identified 40 reports of taxanes used to treat breast, ovarian and lung cancer in pregnant women [Mir *et al.* 2010]. There were no spontaneous abortions or intrauterine deaths, and the only malformation possibly related to taxane exposure was pyloric stenosis in a neonate whose mother had received multi-agent chemotherapy (doxorubicin, cyclophosphamide, paclitaxel and docetaxel). Interpretation of this small body of evidence needs to be done with caution, given the inherent reporting bias.

Long-term effects of chemotherapy exposure

As discussed previously, the potential long-term effects of *in utero* chemotherapy exposure may include gonadal dysfunction and infertility, impaired physical and neurological development and germ-cell mutagenesis resulting in carcinogenesis and teratogenicity in subsequent generations [Partridge and Garber, 2000]. In the breast cancer literature, follow up of children is often short and reports concerning long-term development are uncommon. A single case of malignancy in a child exposed to cyclophosphamide in the

first trimester has been reported [Zemlickis *et al.* 1993]. He was born with limb malformations, abnormal inferior venacava and oesophageal atresia, and developed a thyroid cancer at age 11 years and neuroblastoma at 14 years. However, his fraternal twin had no anomalies.

In a cohort of 84 children born to mothers who were treated with combination chemotherapy during pregnancy for haematological malignancies, normal physical, neurological and psychological development were observed, with absence of malignancy [Avilés and Neri, 2001]. The children's ages ranged from 6 to 29 years at the time of assessment (median 18.7 years). Foetal cardiotoxicity following transplacental transfer of anthracyclines has not been observed to date [Meyer-Wittkopf *et al.* 2001; Garber, 1989; Turchi and Villasis, 1988]; however, long-term follow-up data is again lacking.

Large prospective studies are needed to provide further information regarding the longer-term sequelae of chemotherapy treatment. With this intention, a prospective register of women treated for breast cancer whilst pregnant was initiated by the German Breast Group, and this has been extended by the Breast International Group (BIG 2-03) [German Breast Group, 2010]. In an abstract presented at the European Breast Cancer Conference in 2010, Loibl and colleagues reported that, over a 6.5-year period, 235 patients had been prospectively and retrospectively registered [Loibl *et al.* 2010]. At diagnosis the median maternal age is 33 years (range 23–46 years), with a median gestational age of 23 weeks. The majority of tumours were invasive ductal carcinoma (84%) and high grade (71%), with 50% ER/PR negative and 58.4% HER2 negative. Various anthracycline-based regimens were used, with 11 patients receiving CMF and one receiving a taxane. The median time of delivery was 36 weeks (range 28–42 weeks) with a mean birth weight of 2636 mg (range 1260–3885 mg). Of the 91 newborns exposed to systemic therapy, three had alopecia, one was small for gestational age, one had trisomy 18 and died 1 week after birth, one had necrotic enterocolitis and died 3 weeks after birth, one had temporary apnoea, one developed sepsis, one had neutropenia and two had anaemia. Of note, many of these patients have been included in other published case series.

Endocrine therapy

As previously described, the majority of breast cancers diagnosed in pregnant women are ER negative [Aziz *et al.* 2003; Bonnier *et al.* 1997; Ishida *et al.* 1992]. However, for those women whose tumours are hormone-receptor positive, groups have questioned whether endocrine therapy would be effective and safe during pregnancy. There is evidence from animal studies that tamoxifen may potentially be teratogenic [Furr *et al.* 1976], and data from 50 pregnancies in which the mother took tamoxifen revealed 10 foetal abnormalities, including 2 craniofacial defects [Saunders, 1999]. Other rare foetal abnormalities, including Goldenhar's syndrome (oculoauriculovertebral dysplasia) and ambiguous genitalia, have also been described [Tewari *et al.* 1997; Cullins *et al.* 1994]. There have been reports of the safe delivery of tamoxifen in metastatic breast cancer during pregnancy [Oksüzoglu and Güler, 2002; Isaacs *et al.* 2001]; nevertheless the use of tamoxifen is usually delayed until the end of pregnancy.

Targeted therapies

Studies have shown relatively high rates of HER2-positive tumours in pregnant women, and therefore treatment with trastuzumab may be considered [Aziz *et al.* 2003; Middleton *et al.* 2003; Elledge *et al.* 1993]. However HER2 expression is also high in embryonic tissues, suggesting a role in embryonic neural and cardiac development [Lee *et al.* 1995]. Placental transfer of the monoclonal antibody trastuzumab has been observed in animal studies (Personal communication from Roche Pharmaceuticals, Welwyn Garden City, UK); therefore, its use in pregnancy may not be without risk. Trastuzumab administration for brief periods (i.e. one trimester or less) does not seem to endanger the pregnancy; however, prolonged exposure has been consistently associated with serious adverse events. Many case reports have described reversible oligohydramnios or anhydramnios as a result of exposure to trastuzumab during pregnancy [Azim *et al.* 2009; Beale *et al.* 2009; Warraich and Smith, 2009; Berveiller *et al.* 2008; Pant *et al.* 2008; Witzel *et al.* 2008; Weber-Schoendorfer and Schaefer, 2008; Bader *et al.* 2007; Shrim *et al.* 2007; Sekar and Stone, 2007; Fanale *et al.* 2005; Watson, 2005]. This is believed to be secondary to the effect of trastuzumab on the foetal renal epithelium in which HER2 is strongly expressed [Press *et al.* 1990]. It is also possible that inhibition of the vascular

endothelial growth factor (VEGF) may occur, which regulates the production and re-absorption of the amniotic fluid [Pant *et al*. 2008]. Four neonatal deaths were reported after exposure to trastuzumab *in utero*, secondary to respiratory and renal failure [Beale *et al.* 2009; Warraich and Smith, 2009; Witzel *et al.* 2008; Weber-Schoendorfer and Schaefer, 2008]. Three other neonates developed transient respiratory and/or renal failure but this proved reversible [Beale *et al.* 2009; Bader *et al.* 2007; Shrim *et al.* 2007]. One case report also described exposure to lapatinib, where a patient with metastatic breast cancer inadvertently became pregnancy during lapatinib administration [Kelly *et al.* 2006]. The drug was stopped on week 11 however, and an uncomplicated delivery of a healthy neonate was reported. No cardiotoxicity to the foetus or mother with use of such agents has been reported; however, the long-term implications of exposure to targeted agents in pregnancy are unclear [Robinson *et al.* 2007]. It is therefore advisable that administration of trastuzumab and lapatinib during pregnancy be considered with extreme caution, and in the case of accidental pregnancy, the drug be stopped.

Supportive therapies

Medications such as anti-emetics and steroids can usually be administered during the course of chemotherapy without any adverse effects [Gralla *et al.* 1999]. The 5HT3 antagonists (e.g. ondansetron) have not been reported to cause any malformations [Tincello and Johnstone, 1996; Sullivan *et al.* 1996]. One case–control study has highlighted the association between the use of corticosteroids in the first trimester and the occurrence of cleft palate in the newborn; therefore, steroids are usually avoided in this trimester [Rodríguez-Pinilla and Martínez-Frías, 1998]. Animal studies have not indicated that granulocyte colony-stimulating factor (G-CSF) is teratogenic [Lösch *et al.* 2001]. Two patients in the London-based series received G-CSF while pregnant with no apparent complications [Ring *et al.* 2005b].

Animal studies have not shown any teratogenic effects of the bisphosphonates, pamidronate, although long-term effects on bone growth and development have not been assessed (Personal communication with Novartis Pharmaceuticals UK Limited, Surrey, UK). Two reports describe the use of pamidronate to treat malignant hypercalcaemia during the third trimester of pregnancy [Illidge *et al.* 1996; Dunlop *et al.* 1990]. Postpartum, both neonates suffered from hypocalcaemia, but have subsequently displayed normal development. It is possible that the transient hypocalcaemia occurred as a result of parathyroid suppression in the neonate as a result of the maternal hypercalcaemia, rather than as a direct effect of pamidronate, however careful monitoring of neonatal serum calcium is suggested. A systematic review of 51 patients exposed to bisphosphonates in different indications shortly before or during pregnancy, did not report any foetal adverse events [Djokanovic *et al.* 2008]. Likewise a report on 21 women treated for osteoporosis during the first trimester did not show any adverse events for the foetus of the pregnancy [Levy *et al.* 2009]. The long-term effects of pamidronate on bone growth and development in the neonate are not known.

Prognosis

Pregnancy-associated breast cancer has long been regarded as having a poor prognosis, with the earliest reports describing 5-year survival rates of less than 20% [White, 1954]. This poor prognosis was thought to reflect delay in diagnosis, thereby patients presenting at a more advanced stage [Ishida *et al.* 1992], or that pregnancy itself was an independent predictor of worse survival [Bonnier *et al.* 1997]. However, many of these early studies did not adjust for prognostic variables such as age, stage, pathological features and treatment effect. Several studies have indicated that the prognosis for pregnant patients may not be worse than for age- and stage-matched nonpregnant controls [Aziz *et al.* 2003; Berry *et al.* 1999; Ezzat *et al.* 1996; Lethaby *et al.* 1996; Zemlickis *et al.* 1992a], although one recent retrospective evaluation of 797 patients from the California Cancer Registry did report a higher risk of death compared with controls (39.2% *versus* 33.4%, $p = 0.002$).

Owing to previous beliefs that the hormonal milieu of pregnancy promoted the growth of breast cancer, it was often proposed that termination of pregnancy should be carried out [Petrek, 1994]. However in recent studies, no significant reduction in relapse rate or improvement in survival has been seen with termination of pregnancy [Gemignani *et al.* 1999; Clark and Chua, 1989; Nugent and O'Connell, 1985; White, 1954]; therefore, this is not routinely

recommended to women. However, patients and their relatives must be provided with adequate counselling in order that they can make an informed rational decision in these very difficult circumstances.

Conclusions

Fortunately, the diagnosis of breast cancer during pregnancy is uncommon; however, such women require a tailored approach to treatment with careful consideration given at all stages to the needs of the mother and risks to the foetus. Management is critically influenced by the stage of pregnancy. In particular, during the first trimester there may be significant risks to the foetus, and options both in terms of investigations and treatment may be limited.

It appears that anthracycline-based chemotherapy can be administered during the second and third trimesters, with apparently few short-term implications. Taxanes have also been given with few adverse events at this stage, but the data regarding these agents are very limited. Weekly fractionation regimens may also allow closer monitoring of pregnancy with prompt termination of agents if necessary. However, data concerning the long-term risks of systemic anticancer treatment are limited. Ultimately, all stages of the management of the patient should be discussed within a multidisciplinary team in order that a consensus is reached and clear treatment options are communicated to the mother. Delaying chemotherapy until after delivery may be reasonable in some circumstances, but where the delay is likely to be prolonged, a decision must be made on the basis of the likely balance of risks and benefits.

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Conflict of interest statement

The authors declare no conflict of interest in preparing this article.

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