Breast cancer and pregnancy

A. E. Ring¹,², I. E. Smith² & P. A. Ellis¹*

¹Guy’s Hospital; ²Royal Marsden Hospital, London, UK

Received 26 January 2005; revised 16 April 2005; accepted 31 May 2005

Background: The management of women who have breast cancers diagnosed whilst they are pregnant is challenging. The aim is to give optimal treatment to the mother to maximise the chances of survival, whilst minimising the risks of harm to the fetus. However, few breast surgeons or oncologists develop expertise in this area owing to the rarity of the association.

Design: In this review we evaluate and summarise the current literature regarding the diagnosis, management and prognosis of pregnancy-associated breast cancer. Data were identified by searches of Medline, PubMed and references from relevant articles for the period from 1966 to 2004. Papers were selected based on their size and adequacy of design.

Results: There is a lack of controlled data concerning the management of pregnancy-associated breast cancer. The data available suggest that diagnosis and surgery may be carried out as for the non-pregnant patient, with some limitations on staging investigations. Radiotherapy is contraindicated during pregnancy although, in terms of immediate complications, chemotherapy can be used after the first trimester.

Conclusions: Data from prospective databases that are currently recruiting will provide further important information concerning the management of this condition, and in particular the long-term sequelae for mother and fetus.

Key words: breast cancer, chemotherapy, pregnancy

Introduction

It has been estimated that up to 3% of breast cancers may be diagnosed in pregnant women [1]. Breast cancer associated with pregnancy presents the clinician with particular challenges. The diagnosis may be delayed and difficult owing to the physiological changes within the breast and limitations on investigations. Moreover once a diagnosis has been confirmed and staging completed, options for treatment will be influenced by the need to give optimal treatment to the mother whilst minimising risks to the fetus. The particular challenges faced both in the initial diagnosis and management of women with pregnancy-associated breast cancer are discussed in this paper.

Methodology

Data for this review were identified by searches of PubMed using the keywords ‘breast cancer and pregnancy’, ‘chemotherapy and pregnancy’ and ‘radiotherapy and pregnancy’. The period from 1966 to 2004 was used, and searches were restricted to the English language. References from relevant articles were also selected. Papers were chosen based on their size and adequacy of design.

Diagnosis and staging

The physiological changes occurring in the breast during pregnancy may mean that clinical examination becomes more difficult as pregnancy progresses. Contrary to popular belief, mammography with abdominal shielding can be performed during pregnancy with minimal risk [2, 3]. It has been estimated that a standard two-view mammogram of each breast subjects the fetus to only 0.004 Gy of radiation [2]. However, the increased breast density seen in premenopausal women, together with the physiological changes within the breast during pregnancy, may mean that mammograms are difficult to interpret [3]. Small series report mammographic abnormalities in 63–87% of patients with pregnancy-associated breast cancer [4–6]. On the other hand, ultrasound represents a simple, sensitive alternative to mammography in pregnant and lactating women, and in two small series has been shown to be more sensitive than mammography [4, 5]. In our view, therefore, mammography should rarely be necessary in the investigation of breast cancer in the pregnant woman.

During pregnancy and lactation atypical cytomorphologic features are seen in normal breast tissue, and therefore interpretation of samples acquired by fine needle aspiration needs to be performed with caution [7]. Therefore, core-needle biopsy may be a more appropriate initial procedure, particularly if (as is usually the case) a palpable mass is present. With any interventionald procedure performed on the breast of a pregnant woman
there is a risk of milk fistula formation, and there are higher rates of bleeding and infection [8]. These risks can be minimised by stopping breastfeeding prior to the biopsy, the use of prophylactic antibiotics and paying close attention to haemostasis [8].

Many routine staging investigations used in non-pregnant women use ionising radiation and therefore involve a potential risk to the fetus. The consequences of prenatal exposure to ionising radiation will depend on the dose of radiation, its distribution and the stage of fetal development at the time of exposure [9]. Irradiation in the peri-implantation and early post-implantation period (up to 8 days) may lead to embryonic death [10]. During organogenesis (up to 8 weeks) the fetus is at its most sensitive to radiation-induced malformations, which may occur with exposure to more than 0.05 Gy [10]. Other risks to the fetus when exposed to ionising radiation during this period include intrauterine growth delay, microcephaly and mental retardation. The risk of severe mental retardation is dose- and age-dependent, with a threshold between 0.06–0.31 Gy when the fetus is 8–15 weeks, and of ~0.28 Gy when aged 16–25 weeks [11]. Theoretically it is also possible that irradiation may predispose to sterility and subsequent cancers in the child, although long-term follow-up studies would be required to establish the true incidences of these complications [10].

In general, chest X-rays are regarded as safe during pregnancy as the expected fetal doses are less than the thresholds described above [9]. It is reasonable that these be performed, with appropriate shielding, when clinically indicated. It has been estimated that computed tomography (CT) scans of the liver and the pelvis may expose the fetus to mean doses of 0.0036 and 0.089 Gy, respectively [9]. Therefore, CT scans are usually avoided and metastases are sought using alternative imaging modalities such as ultrasonography. There are theoretical risks to the fetus from exposure to the high magnetic fields used to generate a magnetic resonance image (MRI), and the UK medical devices agency recommends avoiding MRI scans during the first trimester until more information becomes available [12]. In addition, the contrast agent gadolinium should be avoided if possible, as it is has been shown to cross the placenta, and its effects on the developing fetus are not known [13]. Bone metastases can be identified using MR of the skeleton, or modified bone scans [2, 14]. Using such approaches to staging it is possible to minimise the risks to the fetus. Nonetheless, it is important that such investigations should only be used where a positive result would alter immediate management.

Clinical and pathological characteristics

From a number of case series the median maternal age at the time of diagnosis of breast cancer during pregnancy is 33–34 years. The median gestational age at diagnosis is 17–25 weeks [15–18]. As in non-pregnant patients, the majority of tumours are invasive ductal carcinomas, with between 80% and 100% of patients presenting with tumours of this subtype [15, 16, 18, 19]. Between 40% and 84% of patients present with poorly differentiated tumours [15–17, 19], although in a case–control study the rate of poorly differentiated tumours did not exceed that seen in matched non-pregnant controls [19]. The incidence of inflammatory tumours probably lies between 1.5% and 4% [20], although some series report higher rates of inflammatory tumours in pregnant patients than in non-pregnant controls [19]. Previous studies have shown that patients with pregnancy-associated breast cancer commonly present with pathological lymph node involvement (56–67%), large tumours and lymphovascular invasion [17, 21]. Studies have shown that pregnant or lactating women may be more likely to present at a more advanced stage than matched non-pregnant controls [6, 19, 21].

A common finding in series of patients with pregnancy-associated breast cancer is a high frequency of estrogen-receptor (ER)-negative tumours. Between 54% and 80% of pregnancy-associated breast cancers are ER-negative [15, 17, 19, 22, 23]. ER-negative tumours are recognised to be more common in younger women anyway, but in case–control studies ER-negative tumours have been found to be more common in pregnant patients than in age-matched controls [19, 22]. Using a variety of antibodies and scoring systems HER2 positivity has been recorded in 28% to 58% of pregnancy-associated breast cancers [17, 22, 23]. The numbers in these studies are too small to conclude whether the frequency of HER2 positivity is higher than that seen in age-matched controls [22, 23].

Treatment options

Surgery

Surgery is usually the first treatment considered for patients with breast cancer. Limited procedures may be performed under local anaesthesia, but for the majority of patients a general anaesthetic is necessary. In women who are pregnant general anaesthesia is complicated because of increased blood volume and coagulability, decreased lung capacity, slow gastric emptying and supine positional hypotension. One study described 5405 operations performed on a population of 720 000 pregnant women and found that pregnant women undergoing surgery were more likely to have low birth weight infants as a result of both prematurity and intrauterine growth retardation [24]. There were also increases in neonatal mortality, but no increase in congenital malformations or stillbirths. It is not possible to tell whether the adverse outcomes recorded were due to the surgery, anaesthesia or the underlying conditions requiring the procedure to be undertaken. However, small case series suggest that breast-conserving surgery, mastectomies and axillary surgery can all be performed safely with no unexpected complications [15, 16]. The safety of sentinel lymph node biopsy in pregnant patients is not known.

Radiotherapy

The radiation doses used in cancer therapy are much higher than those used in diagnostic radiology, exposing the fetus to considerable risk of toxicity. Using careful fetal dose evaluation it may be possible to irradiate some parts of the mother without significantly irradiating the fetus. In terms of adjuvant breast radiotherapy, fetal dose exposure may be as low as 0.036–0.038 Gy
when completed by the sixth week of gestation [25], but exposure may increase markedly later in pregnancy as the fetus moves closer to the radiation field [26]. These exposures may still put the fetus at risk, and therefore adjuvant breast radiotherapy is usually delayed until after delivery. Unfortunately, delays in delivering adjuvant radiotherapy exceeding 8 weeks in women not receiving systemic therapy may impact on maternal outcome [27]. Under these circumstances this issue will need to be discussed with the patient. However, practically, the need to delay adjuvant radiotherapy until after delivery is rarely an issue as the young age of the patients and high incidence of adverse prognostic features means that adjuvant chemotherapy is often offered in the interim.

Chemotherapy

Maternal effects of chemotherapy. The physiological changes observed in pregnancy may alter the pharmacokinetics and pharmacodynamics of chemotherapy in the mother. In the pregnant woman there are alterations in hepatic metabolism, renal plasma flow and plasma protein binding, all of which may affect drug clearance [28]. The amniotic fluid may also act as a pharmacological third space and delay elimination of agents such as methotrexate. These effects make it difficult to predict the appropriate dose to be administered, and may increase the chances of both maternal and fetal toxicity.

Fetal effects of chemotherapy. The effects of cytotoxic chemotherapy on nucleic acid synthesis and microtubule function, and the rapid rate of cell division occurring in the fetus mean that it is likely to be particularly susceptible to the effects of chemotherapy. All drugs have the potential to cross the placenta, but the extent of transfer depends considerably on the physical and chemical properties of the agent. Methotrexate and 5-fluorouracil are distributed widely in tissues and fluid spaces, and certainly appear to have the potential to enter the amniotic fluid [29–31]. In contrast, in one study doxorubicin was not detected in amniotic fluid collected 4 and 16 h after drug administration in a woman who was 20 weeks pregnant [32]. Furthermore, in vitro perfusion studies using term placenta have shown only very low levels of transplacental transfer of epirubicin [33]. There are minimal data concerning the transplacental transfer of taxanes. However, it is worth noting that P-glycoprotein is expressed in the human placenta, and its presence may reduce fetal exposure to several antineoplastic agents including paclitaxel [34].

First trimester. When chemotherapy is given in the first few weeks of pregnancy there is a significant risk of spontaneous abortion [29]. Over the rest of the first trimester, the fetus remains at risk of spontaneous abortion and there is the additional risk of fetal malformations as a result of exposure to chemotherapy. The estimated risk of fetal malformations when chemotherapy is given during the first trimester is up to 17% [29–31]. This risk is thought to increase when combination therapy is used, and when chemotherapy is given in conjunction with radiotherapy [31]. There also appear to be differences between agents in terms of their potential teratogenicity with antimetabolites and alkylating agents more likely to be associated with miscarriage and malformations [30, 35]. Given the significant risks to the fetus of first trimester exposure to chemotherapy, treatment during this stage of pregnancy is usually avoided.

Second and third trimesters. Chemotherapy has been more widely used in the second and third trimesters, as organogenesis is complete and fetal malformations are therefore unlikely to occur. The only prospective series is from the M.D. Anderson Cancer Center [15]. In this study 24 women with primary or recurrent breast cancer were treated with doxorubicin 50 mg/m² as a continuous infusion over 72 h, cyclophosphamide 500 mg/m² on day 1 and bolus 5-fluorouracil 500 mg/m² on days 1 and 4, all administered every 3–4 weeks. There were no detectable congenital anomalies and no maternal or fetal deaths. In a retrospective series of 28 pregnant patients treated with chemotherapy for breast cancer at London teaching hospitals there were also no deaths or congenital malformations when chemotherapy was given after the first trimester [16].

Pre-term delivery (under 37 weeks gestation) was recorded in nine children in the London series; in one case this was due to spontaneous onset of labour, but in the remainder it was due to physician intervention [16]. Spontaneous onset of labour and other pregnancy complications such as pre-eclampsia have both been reported previously when pregnant women receive chemotherapy [15, 36]. However, it is not known whether the incidences of these complications are in excess of those in the normal population, and what the contribution of chemotherapy is relative to the effects of the underlying disease. Transient leukopenias have also been described in neonates born to mothers receiving chemotherapy [15, 18]. Myelosuppression occurring around the time of delivery may put both mother and baby at risk of sepsis and haemorrhage, and it is therefore recommended that chemotherapy should be avoided for at least 3 weeks prior to delivery in order that maternal blood counts are optimal [18]. Children exposed to chemotherapy in utero might be expected to be at risk of intrauterine growth retardation. The incidence of this is likely to be underestimated in retrospective series; nonetheless, none of the infants in the London hospitals series and only one of those in the M.D. Anderson series had birth weight below the 10th percentile for gestational age [15, 16].

The relative toxicities of different agents are difficult to assess on the basis of the existing data. All of the patients in the M.D. Anderson series and 16 of those in the London series received anthracycline-based treatment [15, 16]. In terms of peri-partum complications and immediate fetal outcome it appears that these agents can be safely administered to women during the second and third trimesters [15, 16]. This conclusion was also made by Germann et al. [37] in their review of 160 patients who had received anthracyclines during pregnancy. However, the use of other cytotoxic agents also seems possible during the second and third trimesters. Vinorelbine in combination with 5-fluorouracil has been given to three patients in the second and third trimesters with no immediate fetal or maternal complications [38]. Paclitaxel has been shown to be toxic to the fetus in animal
studies but has been used in combination with cisplatin from 28 weeks of pregnancy and in combination with epirubicin from 14 weeks with no unexpected maternal or fetal complications [39, 40]. Docetaxel is also toxic to the fetus in animal studies, but the one report of its use to treat metastatic breast cancer between the 23rd and 32nd weeks of pregnancy showed no specific complications [41].

Long-term effects of chemotherapy exposure. The M.D. Anderson Cancer Center prospective study, the French National Survey and the London hospitals series suggest that in the short-term chemotherapy can be safely administered to women within the second and third trimesters of pregnancy [15, 16, 18]. Whilst this is true for the pre-partum and immediate peri-partum periods, little is known about the long-term effects on the fetus of in utero chemotherapy exposure. One could postulate that fetal exposure to chemotherapy may lead to gonadal damage and later problems with fertility, germ cell damage, and higher rates of malignancy and teratogenicity in subsequent generations. Similarly, damage to organs such as the heart, kidneys or central nervous system may not manifest itself as physical or neurological impairment until later in life. In reality, there are very few reports documenting the long-term follow-up of children exposed to chemotherapy in utero. Aviles and Neri [42] described a cohort of 84 children born to mothers who were treated with combination chemotherapy during pregnancy for haematological malignancies. The children’s ages ranged from 6 to 29 years (median 18.7) at the time of assessment, and 12 second-generation children were included in the analysis. Normal physical, neurological and psychological development was observed in all children and there were no reports of malignancies in this cohort. Reports such as this are reassuring but large prospective studies such as that initiated by the German Breast Group [43] and recently extended by the Breast International Group (BIG 2-03) are needed to provide further information regarding the sequelae of treatment.

Growth factors

Growth factors are sometimes needed for haematological support, particularly when dose-dense chemotherapy is used; anecdotal reports describe the use of granulocyte colony-stimulating factor during pregnancy without immediate complications [16, 44].

Targeted therapy

Studies have shown relatively high rates of HER2-positive tumours in pregnant women, and therefore treatment with trastuzumab may be considered [17, 22, 23]. However, HER2 expression is also high in embryonic tissues, suggesting a role in embryonic development, and placental transfer of the monoclonal antibody trastuzumab has been observed in animal studies (personal communication from Roche Pharmaceuticals, Welwyn Garden City, UK). Therefore, the use of the trastuzumab during pregnancy cannot currently be recommended.

Endocrine therapy

There is evidence from animal studies that the selective ER modulator tamoxifen may potentially be teratogenic [45]. Data from 50 pregnancies in which the mother took tamoxifen revealed 10 fetal abnormalities, including two craniofacial defects [46]. Other rare fetal abnormalities, including Goldenhar’s syndrome (oculoauriculovertebral dysplasia) and ambiguous genitalia, have also been described [47, 48]. Therefore, the use of tamoxifen is usually delayed until the end of pregnancy.

Bisphosphonates

Bisphosphonates are frequently used in the management of skeletal complications from metastatic breast cancer and have an emerging role in the adjuvant setting. Two reports describe the use of pamidronate to treat malignant hypercalcaemia during the third trimester of pregnancy [49, 50]. Post-partum, both neonates suffered from hypocalcaemia, but have subsequently undergone normal development. It is possible that the transient hypocalcaemia occurred as a result of parathyroid suppression in the neonate caused by maternal hypercalcaemia, rather than as a direct effect of pamidronate on the fetus [49, 50]. Nonetheless, the authors recommend that in the rare instances where bisphosphonates are used in pregnant patients neonatal calcium should be carefully monitored [49]. The long-term effects of pamidronate on bone growth and development in the neonate are not known.

Termination of pregnancy

Termination of pregnancy is an option sometimes considered by pregnant women who are diagnosed with breast cancer. In the past this option was recommended in the belief that the hormonal changes of pregnancy promoted the growth of breast cancer. In historical series no significant reduction in relapse rate or improvement in survival has been seen with termination of pregnancy [1, 20], but it is possible that any potential benefit from termination was masked by a tendency for women with worse prognoses to opt for this, or by a high rate of hormone receptor-negative tumours. It may still be reasonable to discuss termination if the fetus is likely to be exposed to significant risk of harm by potentially curative treatment given to the mother. In addition, some women with metastatic or high-risk cancer may not want to carry on with the pregnancy. 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.

Prognosis of pregnancy-associated breast cancer

Pregnancy-associated breast cancer has long been regarded as having a poor prognosis, with the earliest reports describing 5-year survival rates of <20% [1]. However, in a more recent study
overall survival of patients with stage II and III disease was found to be 75% (at a median of 40 months), suggesting that with modern multimodality therapy outcome may not be as poor as was previously thought [15]. The previously observed poor prognosis was thought to be partly explained by a tendency for pregnant patients to present at a more advanced stage than non-pregnant women, possibly reflecting delay in diagnosis [6, 19]. However, late stage at diagnosis may not be the only explanation for the poor prognosis observed; it has been proposed that pregnancy itself may be an independent predictor of worse survival [19]. Many of the earlier studies that documented poor survival rates failed to adjust for age, stage, pathological features, treatment effect and other established prognostic variables. Where case–control studies have been carried out, most suggest little difference in survival between pregnancy-associated and non-pregnancy associated breast cancer [21, 22].

Conclusions

Women who are diagnosed with breast cancer during pregnancy require a tailored approach to management with careful consideration given at all stages to the needs of the mother and risks to the fetus. Data concerning the long-term risks of surgery, radiotherapy and systemic anticancer treatment are limited. Management is critically influenced by the stage of the pregnancy. In particular, during the first trimester there may be significant risks of fetal damage, and options both in terms of investigations and treatment may be limited. However, current data concerning the short-term safety of surgery and chemotherapy administered during the second and third trimesters are reassuring. At all stages the management of the patient should be decided by a multidisciplinary team, incorporating not only breast surgeon, medical and clinical oncologists, but also obstetricians, neonatologists and specialist nursing staff in order to ensure the best possible outcome for both mother and infant.

References