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Focus On

Breast cancer and pregnancy

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Abstract Breast cancer is one of the most commonly diagnosed cancers in pregnant women. Diagnosis and treatment in these women are particularly challenging as the necessary investigations and treatment modalities may potentially harm the developing foetus. Nonetheless, it appears that initial diagnostic investigations may be carried out as for non-pregnant women, but bearing in mind the risks of exposing the foetus to ionising radiation. Surgery can be carried out with little risk to the mother or foetus but radiotherapy is generally avoided. Chemotherapy can be given relatively safely when administered after the first trimester, but large volume prospective data and, in particular, data regarding the long-term implications of *in utero* exposure, are awaited.

Keywords: Breast cancer; Chemotherapy in pregnancy; Pregnancy; Surgery in pregnancy

Epidemiology of breast cancer in pregnancy

It is estimated that 1 in 3000 pregnancies are complicated by breast cancer, and the incidence is expected to rise as more women in developed countries delay childbearing until later in life [1–5]. There is no consensus in the literature as to what comprises 'pregnancy-associated breast cancer', with some authors including only breast cancers diagnosed in women who are pregnant at the time of diagnosis, and others also including breast cancers diagnosed within a year postpartum or during lactation.

Principles of treating breast cancer in pregnant women

An appreciation of the stages of *in utero* development is critical to the appropriate management of these patients. Implantation usually occurs within two weeks following conception. In humans the internal organs develop their structure within the third to eighth weeks *in utero* (the period of organogenesis). Insults, pharmacological or physical, to the foetus during this period may manifest as major malformations, or as foetal loss. However, after the first trimester organogenesis is complete and the risks of major malformations are minimal, although it should be recognised that the gonads and the central nervous system continue to develop later in foetal life. The rest of uterine life largely consists of growth and maturation of the foetus, processes that appear to be less-obviously susceptible to the effects of pharmacological and physical damage.

Diagnosing breast cancer in pregnant women

As for non-pregnant women, the diagnostic pathway should comprise clinical examination, imaging and pathological assessments. However, during pregnancy, clinical breast examination can be difficult as the breasts become firmer and more nodular as a result of glandular proliferation. Mammograms

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are often not performed, not just because of concerns regarding harm to the foetus from ionising radiation, but also because the increased breast density in pregnancy makes them more difficult to interpret. (However, it should be recognised that mammography may identify extensive microcalcifications, a finding that may alter management if a wide-local excision is being considered.) Ultrasound is more frequently used as the imaging modality of choice, particularly as most women present with a lump. There is very limited data concerning the utility of magnetic resonance imaging (MRI) to diagnose primary breast cancers, and there are difficulties with positioning the patient prone and concerns regarding the safety of gadolinium contrast agent [6].

Staging investigations should be carried out where appropriate, taking into consideration the risks to the foetus and the extent to which a positive result will immediately effect management. The issue of exposure to ionising radiation in pregnancy is one which creates a great deal of concern among physicians and patients, but in fact when one considers chest X-rays and mammograms the risks are probably minimal [7,8]. However, CT scans may expose the foetus to higher doses of radiation and are usually avoided. Metastases may be sought using other imaging modalities such as ultrasonography or MRI [9].

Histopathological features of breast cancer in pregnancy

In pregnant women, the histopathological and immunohistochemical findings of breast cancer are found to be similar to those of non-pregnant young women, indicating that the biological features of the cancer are most likely determined by the age of the patient at diagnosis [10]. A large proportion of the tumours diagnosed during pregnancy are high grade, display lymphovascular invasion and involve the axillary lymph nodes [10–12]. Approximately 60–80% of breast cancers during pregnancy are reported to be oestrogen receptor (ER) negative and between 28% and 58% are said to be HER2 positive [13]. These features are similar to those we would expect in pre menopausal non-pregnant women.

Treatment of pregnancy-associated breast cancer

The treatment of a woman diagnosed with breast cancer while pregnant presents a challenge to all of those involved in their care. The data we currently use to make management decisions in pregnancy-associated breast cancer are incomplete and continue to evolve. However it is possible to draw some conclusions from the information that we do have. The treatment offered depends on the stage of the cancer, the gestational age at first presentation and patient preferences.

Surgery

Surgery is the first line of treatment for most women with breast cancer, including those who are pregnant. Breast surgery, including general anaesthesia, can be performed with minimal risk to the foetus at all stages of pregnancy [14,15]. Historically, most pregnant women were offered a mastectomy owing to high local recurrence rates and in the hope of avoiding adjuvant radiotherapy, which is relatively contraindicated in pregnancy [12,16]. However, increasingly young women are offered postoperative adjuvant chemotherapy while pregnant with radiotherapy delayed until after delivery, meaning that breast-conserving surgery has become a reasonable option. An alternative approach is to offer neoadjuvant medical therapy in pregnancy and delay surgery until postpartum [17,18]. Depending on gestational age and patient preferences, this may be a very reasonable option. The safety of sentinel lymph node biopsy in pregnancy is unknown. Some studies suggest that the amount of radiation delivered through the use of technetium for a sentinel node biopsy is as low as 4.3 mGy and could be offered to patients [19,20].

Systemic treatment

Data on the use of chemotherapy during pregnancy are limited to case reports and small case series. It appears that most anti-neoplastic drugs have the potential to cross the placenta, and by virtue of their mechanism of action could potentially harm the foetus. A second major consideration is that physiological changes associated with pregnancy affect drug pharmacokinetics and complicate correct dosing of chemotherapy agents, such that not only may the foetus be put at even greater risk but also the mother may not be treated optimally.

One might predict from knowledge of *in utero* development that the foetus would be at greatest risk of harm in the first trimester, and in particular during organogenesis. Indeed, when chemotherapy is given during the first trimester, the risk of malformations is approximately 10–20% [21–23]. However, when chemotherapy is administered in the third trimester, the rate of congenital malformations has been reported as approximately 3%, which is similar to the baseline population risk of major malformations [24]. Hence, chemotherapy

is usually avoided during the early embryonic period due to potential damage to the foetus. Chemotherapy-related problems are not just restricted to intra-uterine life, there can be a potential risk of sepsis and haemorrhage if the mother develops bone marrow suppression secondary to treatment and then delivers the baby. Neonatal cytopenias have been reported concomitantly with maternal low blood counts, which can pose a significant risk for the newborn [25]. Hence, delivering chemotherapy even in the second and third trimesters can sometimes prove potentially dangerous.

The regimens for which the most information is available are the anthracycline-based regimens. The MD Anderson series is a prospective body of evidence which shows that fluorouracil, Adriamycin and cyclophosphamide (FAC) chemotherapy can be given in the second/third trimester of pregnancy with minimal risk to the foetus, assuming that chemotherapy is not administered around the time of delivery [26]. There is minimal data available concerning the use of taxanes in pregnancy-associated breast cancer, but a handful of case reports indicate no greater risk with use of taxane-based preparations [13,27]. The potential implications of *in utero* chemotherapy exposure for long-term neurological, educational and cardiac development in the offspring, and also in the fertility of the offspring, are unknown. It is incumbent upon us to continue to improve the limited knowledge we have regarding this issue. The way to tackle this situation is through observation and reassessment of outcomes of pregnant women who received chemotherapy for breast cancer through national and international registry studies.

Trastuzumab has been used in the treatment of pregnancy-associated breast cancer without any adverse effects [28], and with reversible anhydramnios and renal failure [29]. However, the long-term implications of exposure to this and other targeted treatments in pregnancy are unclear [30]. Hormonal treatment, if indicated, is usually deferred until after delivery. Some case reports highlight the safe delivery of tamoxifen in metastatic breast cancer [31,32], whereas others report birth defects like Goldenhar syndrome [33] and ambiguous genitalia [34].

Medications like anti-emetics and steroids can usually be administered during the course of chemotherapy without any adverse effects [35]. 5HT3 antagonists like ondansetron have not been reported to cause any malformations [36,37]. 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; hence, steroids should probably be avoided in the first trimester [38]. Granulocyte colony-stimulating factors (GCSF) and erythropoietin have been safely used in pregnancy and the current recommendations for the use of white blood cell growth factors should be followed [39,40].

Radiotherapy

As with any ionising radiation exposure, there is the risk with radiotherapy of inducing foetal loss, malformations or growth retardation. In the treatment of breast cancer, a standard dose of 50–60 Gy is used to radiate the breast tissue/chest wall and the foetus could receive up to 2 cGy in the first trimester, 24.6 cGy in the second trimester and up to 58.6 cGy in the third trimester [7]. Radiation doses of 10–90 cGy have been associated with detrimental consequences [41]. Therefore in pregnancy-associated breast cancer radiotherapy is usually deferred till after delivery. However, there have been some reported cases of radiotherapy use in pregnant breast cancer patients [42]. Under these circumstances, the potential of radiotherapy to harm the foetus has to be weighed up against improvements in recurrence-free survival and overall mortality from breast cancer.

Genetic counselling

Up to 10% of breast cancers have an inherited basis. These cancers may occur as a result of inheriting an altered BRCA1 or BRCA2 gene. Women with a mutation in either gene are at an increased risk for early-onset breast cancer, bilateral breast cancer and ovarian cancer. Women with pregnancy-associated breast cancer have an increased risk for these predisposing mutations, hence genetic counselling is recommended for all these women. In one Swedish study, more women with pregnancy-associated breast cancers had a BRCA1 mutation rather than a BRCA2 mutation [43]. Genetic counselling combined with genetic testing may help women to make important decisions about medical care and cancer screening.

Psychological counselling

The diagnosis of breast cancer during pregnancy will certainly cause shock, anxiety and depression to any woman and the members of her family. Patients should be offered the opportunity to discuss some of the complex decisions in a supportive environment with a skilled counsellor, especially if they have difficulty coping with making major life decisions sooner than expected. Also, getting such women in contact with other younger women who have pregnancy-associated breast cancer may help.

Prognosis of breast cancer in pregnancy

Historically, pregnancy-associated breast cancer has been assumed to have a particularly poor prognosis, with 5-year survivals in the region of 20–30%. However, initial case series were not necessarily compared with appropriate matched control cases, taking into account important patient and pathological variables, such as young age, grade of tumour and ER status. Where this has been done, and if one makes allowances for the fact that many of these women did not receive optimal treatment, there is probably little difference in survival between pregnancy-associated and non-pregnancy-associated breast cancer [44–46].

Discussion

The treatment of women with breast cancer diagnosed in pregnancy poses a unique challenge to the health care professionals involved in their care. Treatment should be instigated by the multidisciplinary team such that a consensus to management is made. Initial investigations can be carried out as for non-pregnant women bearing in mind the adverse effects of ionising radiation to the foetus. Surgery can be carried out without much risk, but radiotherapy is generally avoided. Chemotherapy can be administered safely after the first trimester but is avoided around the time of delivery in order to prevent complications related to cytopenias. Under these circumstances there is little evidence to suggest that chemotherapy has significant short-term implications for the foetus or the mother, but the long-term implications of such exposure remain unknown.

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