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Case Study

A case of Triple Negative Breast Cancer diagnosed

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Key Learning Points

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Breast cancer is the commonest malignancy affecting women, with a lifetime risk of 1 in 8. Although a full-term pregnancy at a young age is protective against developing the disease, a diagnosis of breast cancer during pregnancy or lactation is associated with increased cause-specific mortality.

While a cancer diagnosis during pregnancy is not common, this case highlights the complexity of diagnosing and managing patients with pregnancy-associated breast cancer, as well as the relevant prognostic challenges.

Our knowledge of diagnosing and managing patients with pregnancy-associated breast cancer has been increasing, with improving outcomes. Many of the recognised standard cancer treatments can still be used, with certain caveats depending on the stage of the pregnancy. Babies do not need to be delivered early, avoiding the morbidity and mortality associated with prematurity. Multidisciplinary specialist input, however, is essential, and patients with pregnancy associated breast cancer need close monitoring in the first years postpartum.

Keywords:
Breast cancer, Pregnancy, Triple negative.

Introduction

Mrs DS is a 33-year old lady, mother of a 2-year-old daughter and 24 weeks into the pregnancy of her second child. She had been referred to our breast clinic after noticing a palpable lump in her left breast on self-examination two weeks previously, which raised significant apprehension in her, especially after the loss of her first husband to osteosarcoma 12 years ago.

Mrs DS is normally fit and well, is on no regular medications, has no known drug allergies, and does not smoke or drink alcohol. She has no family history of breast or ovarian cancer. She was on the oral contraceptive pill before her two intended pregnancies, and she breastfed her first child for 12 months. On clinical examination, her breasts displayed no obvious asymmetry, lumps, skin changes or nipple changes. Palpation revealed no obvious enlargement of the lymph nodes in her neck or armpits. Both breasts presented with the characteristic lumpiness of lactational changes, and, although a mass of about 2 cm in diameter could be palpated in the upper outer quadrant of her left breast, the extent of lumpiness was of hindrance to the confident characterisation of the lump. Being mammography unsuitable for young women, Mrs DS was referred for ultrasound scan of her breasts and axillae. Imaging revealed normal right breast and axillary lymph nodes bilaterally and confirmed the palpable mass in the left breast to be an indeterminate lobulated lesion, possibly a fibroadenoma, 22x18x16 cm in size. However, ultrasound-guided core biopsy of the mass revealed that this was a grade 3 invasive ductal carcinoma. Immunohistochemistry reported oestrogen receptor staining of 3/8, progesterone receptor staining of 3/8, and negative amplification of human epidermal growth factor receptor 2, which phenotypically classify this lesion as a triple negative

breast cancer (TNBC).

When informed of her results, Mrs DS was clearly upset but took the news bravely. She decided to continue the pregnancy and undergo treatment for her cancer with the opportune precautions to protect her baby. After prolonged consultation with the multidisciplinary care team (MDT), Mrs DS decided to undergo prompt surgery for removal of her cancer and has since undergone a wire-guided circumareolar mammoplasty and sentinel lymph node biopsy with radioisotope but not blue dye, which has unclear teratogenic potential. The procedures were successful, with no immediate or early adverse effects on the patient and her foetus, as confirmed by ultrasound foetal heart beat check before and after surgery. If histopathology confirms clear margins and a second operation is not necessary, the current plan is for Mrs DS to be referred to the oncologists for chemotherapy in the third trimester and deliver naturally, ideally at term; she would then continue adjuvant treatment with both chemotherapy and radiotherapy postpartum. Furthermore, Mrs DS has been referred for genetic testing for BRCA mutations, despite the lack of family history for breast and ovarian cancer, due to her young age and the triple-negative nature of her breast cancer.

Therapeutic approach to cancer diagnosed during pregnancy

A diagnosis of cancer is always emotionally devastating, and even more so during pregnancy, when the joy of a new life is eclipsed by the fear of death. The situation also represents a medical dilemma, as a careful balance must be established between the best treatment for the mother and its impact on the foetus, which often are conflicting. The complexity of dealing with two patients at once requires the contribution of an MDT including breast surgeons, oncologists, obstetricians, gynaecologists, specialist nurses, and other healthcare professionals. The current lack of consensus on a standard treatment is such that care is tailored to suite the medical, ethical, legal, personal, emotional, psychological, and religious circumstances of each case, with the patient at the centre of and actively contributing to the decision-making process. However, despite the growing body of evidence, comprehensive data on cancer diagnosed during pregnancy is still limited, and an understanding of our current knowledge, and importantly the current gaps in our knowledge, is key for both the clinical team and the patient to make an informed decision on treatment options.

The National Institute for Clinical Excellence (NICE) has accredited the Breast & Pregnancy Green-top Guideline No. 12 published by the Royal College of Obstetricians & Gynaecologists in March 2011[1]. Treatment strategies are different in the three trimesters. Breast surgery, usually either mastectomy or wide local excision with or without axillary clearance, has been demonstrated to be safe during pregnancy, especially during the second trimester, provided that opportune precautions are in place to provide optimal care for both the mother and the foetus[2]. For example, regional anaesthesia is preferred to general anaesthesia where possible (although no anaesthetic agents have been shown to be teratogenic) and normal maternal physiology should be maintained to optimise uteroplacental perfusion and avoid foetal asphyxia, especially in the delicate early stages of embryonal development. Notably, whereas radioisotope scintigraphy for sentinel lymph node tracing has been proven to be safe during pregnancy due to the insignificant amount of uterine radiation, blue dye is not recommended as its effects on foetal development have not been sufficiently investigated[3].

The administration of radiotherapy during pregnancy is controversial and not recommended due to the teratogenic effects of ionising radiation on the developing foetus, which include but are not limited to neurodevelopmental defects, physical malformations, and death in utero[4]. This concept, mostly deriving from major nuclear accidents, is widely accepted and applied in clinical practice for all forms of ionising radiation[5], and radiotherapy is administered only to a minority of pregnant cancer patients. Although some studies claim that, with opportune precautions, radiotherapy may be achieved without significant adverse outcomes for the foetus[6], evidence for this is mostly drawn from isolated exposure accidents, and the absence of larger studies, which would be ethically unjustifiable, means that radiotherapy is commonly postponed to the postpartum period. Similarly, the administration of targeted therapies such as monoclonal antibodies, hormonal treatments, and tyrosine kinase inhibitors during pregnancy is rare in clinical practice and is generally advised to be commenced after delivery due to scarcity of evidence and barriers to the approval of clinical trials[1]. Moreover, it has to be remembered that, due to lack of drug-targetable receptors in TNBC, hormonal treatment is not an option for Mrs DS.

Chemotherapy during pregnancy is contraindicated in the first trimester due to the high rate of foetal abnormalities but is considered safe in the second and third trimesters, with extensive evidence for no adverse foetal, neonatal, and longer-term outcomes on children exposed to chemotherapy in utero in a series of studies published by the groups of Amant and Cardonick[7,8]. One important consideration is that chemotherapy should be discontinued at least 2-3 weeks before delivery to minimise complications secondary to neutropenia during maternal bone marrow suppression[1]. Concerning breast cancer diagnosed during pregnancy, most cases are treated with combination chemotherapy regimens such as FAC (5-fluorouracil, doxorubicin, and cyclophosphamide) that can be administered both as neoadjuvant and adjuvant options. However, as the Cancer and Pregnancy Registry (established by Cardonick to collect data on cancer during and after pregnancy) grows, evidence is being accumulated on the safety of more chemotherapeutic agents including taxanes[9].

The Lancet recently featured a cohort study that analyses the oncological management and obstetric and neonatal outcomes for 1170 women diagnosed with all cancers during pregnancy in 16 countries from 1996 to 2016. 779 (67%) received treatment during pregnancy, most commonly surgery or chemotherapy or a combination of the two. Overall, 99% of singleton pregnancies ended up in livebirth, half of which prematurely; importantly, about 90% of the preterm deliveries were iatrogenic[10]. This is unacceptable, as the long-term negative impact of prematurity on cognitive development has been demonstrated repeatedly in the literature[11]. Importantly, the increase in neonatal mortality (incidence ratio 2.7, 95% CI 1.3–5.6) in babies born from patients with cancer during pregnancy was found to be independent of cancer treatment and attributable to prematurity in 90% of cases[12,13]. However, it is important to note that multiple regression revealed a relationship between some forms of chemotherapy, namely platinum-based agents and taxanes, and adverse neonatal outcomes such as small for gestational age and neonatal intense care unit (NICU) admissions[10]. Although there

was not a corresponding increase in neonatal mortality, this questions previous literature on safety of antenatal chemotherapy, highlighting the need for further research.

The cohort study published by the Lancet is one of the first large, internationally-coordinated attempts at systematically collecting data on cancer diagnosed during pregnancy and offers essential insights into the trends characterising this rapidly evolving field. Every 5 years there was a small, yet statistically significant, increase in the likelihood of livebirth for singleton pregnancies (relative risk (RR) 1.04, 95% CI 1.01–1.06) and a reduction in the risk of preterm iatrogenic livebirths (RR 0.91, 95% CI 0.84–0.98), with a corresponding decrease in NICU admissions. Concurrently, there was a rise in the likelihood of patients receiving treatment during pregnancy (RR 1.10, 95% CI 1.05–1.15), which was mainly driven by the increasing administration of chemotherapy (RR 1.31, 95% CI 1.20–1.43); specifically, there was an increase of 2.6 days (95% CI −1.1 to 6.3) in the gestational age of the last chemotherapy cycle given during pregnancy[10]. Although this last result is not statistically significant and is regardless unlikely to have a clinically significant effect on maternal outcomes, it reflects a progressive increase in awareness about the safety and feasibility of cancer treatment during pregnancy. This will hopefully lead, over time, to the same optimum management for pregnant and non-pregnant women, as well as to the avoidance of unjustified termination of pregnancies and induction of premature delivery. An example of this is already provided in a study of 75 breast cancer patients treated with FAC chemotherapy during pregnancy, that shows overall survival (OS) and recurrence-free survival (RFS) comparable to, if not better than, non-pregnant controls who received the same treatment[14]. However, these promising results should be interpreted considering the small sample size of the study.

Prognosis of Pregnancy-Associated Breast Cancer

The prognosis of cancer diagnosed during pregnancy deserves further attention. OS and RFS are well documented for most cancers and are not worsened by pregnancy for many of them when data from pregnant patients are matched for age at diagnosis, extent of disease, and diagnostic times with non-pregnant patients; however, breast cancer stands out as one of the exceptions, together with ovarian cancer, for which diagnosis during pregnancy or lactation seems to increase the risk of cause-specific death[15]. This stands in clear contrast with the well-accepted concept that early full-term pregnancy decreases the lifetime risk of breast cancer. It has been suggested that remodelling of the cellular and extracellular milieu of the breast during pregnancy and involution may contribute to the enhanced invasive and metastatic potential of breast cancer, leading to poorer clinical outcomes[16]. This led to the definition of pregnancy-associated breast cancer (PABC) as breast cancer diagnosed during pregnancy or within 1 year following parturition.

Breast cancer is the most common female cancer worldwide as well as the most common cancer diagnosed in pregnancy. PABC affects up to 1 in 3000 pregnancies, with almost 25,000 new cases yearly worldwide (one third of which diagnosed during pregnancy), and represents up to 10% of breast cancers diagnosed in women younger than 40 years old[17]. As women increasingly delay childbearing, these figures are likely to rise. Although young age per se is associated with more aggressive cancer features, PABC shows more advanced stage at diagnosis, larger size, higher grade, greater nodal involvement and a higher proportion of TNBC compared to age-matched non-PABC cases[18]. This may be due to the physiological changes associated with pregnancy and lactation, which may hide clinical signs and hinder recognition of PABC, delaying diagnosis. The literature, however, is divided on whether PABC carries an intrinsically worse prognosis than non-PABC when matched for known prognostic features.

A meta-analysis of 30 control-matched studies conducted by Azim et al. in 2012 on 3628 PABC cases versus 37,100 non-PABC controls found an overall difference in prognosis, with PABC having reduced OS (RR 1.44; 95% CI 1.27-1.63). However, subgroup analysis highlighted that this difference was mostly driven by patients diagnosed postpartum (RR 1.84; 95% CI 1.28-2.65), whereas OS of cases diagnosed during pregnancy did not significantly differ from controls (RR 1.29; 95% CI 0.74-2.24)[19]. The poorer prognosis for PABC diagnosed postpartum compared to PABC diagnosed during pregnancy was subsequently confirmed in many other studies. Conversely, a cohort study conducted by Amant et al. in 2013 did not find a significant difference in survival for 311 PABC cases compared to 865 non-PABC controls matched for prognostic factors including age, stage, grade, hormonal receptors and type of treatment[20]. It must be noted, however, that this study only included patients diagnosed during pregnancy, disregarding the effect of PABC cases diagnosed postpartum on survival for PABC.

The recognition that cases diagnosed postpartum majorly impact PABC prognosis raised the question of how long after delivery this effect extends. Although no consensus has been reached yet and PABC literature features studies on breast cancer cases diagnosed up to 15 years after pregnancy, 5 years has been suggested as a revised threshold[21]. In fact, the largest meta-analysis on PABC published to date, which comprises 41 (34 case-control and 7 cohort) studies including 4929 cases and a total of 65970 controls, considers cancers diagnosed during pregnancy or within 5 years postpartum[22]. This study reveals that OS and DFS for PBCA diagnosed until 5 years postpartum are similar to those obtained with the conventional definition PBCA compared to controls, confirming that the current definition of PABC may be severely limited. Group sub-analysis shows that overall decrease in OS and DFS is driven mainly by the first 2 years postpartum, with DFS for the pregnancy subgroup being insignificantly lower than DFS for non-PABC controls. However, it must be considered that this meta-analysis pools data from heterogeneous studies that use different definitions of PABC. Interestingly, 21 of the 37 individual studies found a negative or null association between PABC and increased mortality.

Mrs DS's prognosis is also influenced by her cancer subtype. TNBC accounts for 10-20% of all invasive breast cancers and is associated with younger age (<40 years), higher grade, and more advanced stage at diagnosis. Clinically, TNBC has high chemosensitivity but carries a poorer prognosis than other subtypes[23]. A study of 1601 patients shows that TNBC has an aggressive phenotype, with a high risk of local and distant metastasis to lungs and brain in the first 5 years after surgery (during which OS was reduced and most deaths occurred) peaking at 3 years and rapidly decreasing thereafter, as opposed to other breast cancer subtypes that predominantly recur 5-10 years after surgery[24]. TNBC has been associated with germline mutations in the BRCA breast and ovarian cancer susceptibility gene, with 60-80% of breast tumours from BRCA1 mutation carriers displaying a TNBC phenotype[25].

In a cohort of 1824 patients with TNBC unselected for family history of breast or ovarian cancer, the probability of an underlying pathogenic BRCA mutation exceeded 10% in those diagnosed before age 40[26].

As carriers of BRCA mutations have a 50-85% risk of developing breast cancer and a 20-60% of developing ovarian cancer during their lifetime, they are frequently offered prophylactic risk-reducing surgery including bilateral mastectomy and salpingo-oophorectomy to prevent second primary cancers. However, the Prospective Outcomes in Sporadic versus Hereditary breast cancer (POSH) study, which is the largest published prospective cohort study comparing young-onset (<40 years) breast cancer outcomes of 338 BRCA mutation carriers with 2395 sporadic cancer patients, revealed there is no statistical difference in survival between the two groups up to 10 years after diagnosis. Intriguingly, a pre-specified analysis of the 558 patients in the TNBC subgroup revealed that 2-year OS was significantly better for the 136 BRCA-positive patients than for BRCA-negative patients, although there was no significant difference for 5-year OS. To determine whether better OS for BRCA mutations carriers with TNBC was due to the beneficial effect of risk-reducing surgery, a post-hoc analysis excluded the 31 patients who underwent bilateral mastectomy within the first year after diagnosis; however, this was not sufficient to make the difference statistically insignificant (RR 0.52; 95% CI 0.29–0.91)[27]. This finding bears implication for timing of risk-reducing surgery, which has benefits in the long, but possibly not short, term.

Mrs DS's circumstances are very unfortunate. However, it is important to realise that her experience is not unique, as cancer diagnosis during pregnancy is far from rare, and thousands of women go through it every year. The growing awareness of this condition is driving a dynamic field of research, and hopefully large studies will allow the optimisation of cancer management in pregnant women in the near future. Although Mrs DS's TNBC is not amenable to hormonal treatment, chemotherapy is a promising alternative supported by high-quality evidence in the literature. Concerning her prognosis, it is difficult to draw a conclusion. Even though it is unclear if breast cancer diagnosis during pregnancy intrinsically carries a poorer prognosis, Mrs DS also falls into the category of women diagnosed with breast cancer in the first years postpartum, for which evidence for reduced survival is more convincing. Considering this and the recurrence pattern of TNBC, Mrs DS will need to be closely monitored over the next few years as she might be at a high risk of early recurrence. Counterintuitively, a positive result for BRCA mutations may be beneficial for her prognosis in the short term, although how PABC, TNBC, and BRCA interact to affect survival remains unclear. BRCA status may also inform Mrs DS's decision to undertake prophylactic measures in the long term, when the peak risk of recurrence will have passed and a transient reduction in quality of life from recovery after risk-reducing surgery will be justified by a beneficial effect on survival. However, it remains unclear for how many years postpartum there is an increased risk of recurrence before parity starts having a protective effect on survival. Thus, this case prompts further research to clearly define the prognosis of PABC, which is essential for mothers like Mrs DS to make informed decisions on treatment and life.

Conflicts of interest

None.

Funding

None.

Consent

The patient has consented for the publication of this case study.

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