



# A growing dilemma - breast cancer and pregnancy

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**BACKGROUND** Breast cancer and pregnancy are events that have an enormous impact on the lives of women. When these events are associated they become a highly emotive issue with possible devastating consequences.

**OBJECTIVE** While information on breast cancer is widely available, much less is reported on the association between breast cancer and pregnancy. This article reviews the available evidence on which general practitioners can base their management of women with gestational breast cancer or breast cancer survivors who may want to conceive.

**DISCUSSION** Breast cancer can be diagnosed during pregnancy or in the 12 months postpartum (including lactation), known as gestational breast cancer or pregnancy associated breast cancer. Previous treatment for breast cancer may have detrimental effects for women who subsequently conceive or wish to conceive. General practitioners, as the primary care giver, have an integral role in the successful education, management and support of these women.

**B**reast cancer and pregnancy are events that have an enormous impact on the lives of women. An association between breast cancer and pregnancy is uncommon, but can have devastating consequences. The association is likely to become more frequent as childbearing practices change, and more women choose to delay pregnancy until their late 30s and 40s, when the incidence of breast cancer begins to increase. A diagnosis of breast cancer can affect pregnancy in two ways. The first is when a woman is diagnosed with breast cancer during pregnancy or in the 12 months postpartum (including lactation), known as gestational breast cancer (GBC) or

pregnancy associated breast cancer. The second is the effect a prior diagnosis of breast cancer may have on women who subsequently conceive or wish to conceive. General practitioners play an integral role in the successful management and support of these women both in the early detection of breast cancer, education of their patients, and prompt referral to a specialist tertiary centre.

Historically the association of breast cancer and pregnancy was thought to carry a poor prognosis. Gross stated in 1880: '(that) its growth is wonderfully rapid and its course extremely malignant.'<sup>12</sup> This negative view, and the fact that most practitioners' experience of

GBC is limited, has continued to impact upon the medical psyche. Most surgeons and GPs still think the outcome for GBC is very poor.<sup>1</sup> Breast cancer survivors have also been advised against subsequent pregnancy as it was thought the hormonal stimulation would lead to a worse breast cancer outcome.

## Gestational breast cancer

### Incidence and outcomes

The reported incidence of GBC ranges from 0.7-3.8% of all diagnosed breast cancers.<sup>3,7</sup> Overall the incidence appears low, but as it only affects premenopausal women the true incidence of GBC is reported to be between 7-14% of pre-

**Table 1. Differential diagnosis of breast symptoms in pregnancy**

- Lactational abscess
- Galactocele
- Enlarging fibroadenoma
- Physiological changes
- Cancer

menopausal breast cancers.<sup>2,8,9</sup> In the Australian population this means approximately 200 women per year are diagnosed with GBC.

Gestational breast cancers have been shown to have a worse prognosis and are more advanced at presentation (larger tumours and lymph node positive) than nongestational breast cancers.<sup>10-13</sup> However, when age and stage are taken into account there is no difference in survival between gestational and nongestational breast cancers. Ezzat reports a seven year overall survival for GBC of 57% (95% CI: 33-81) and for non-GBC 61% (95% CI: 47-75), which was not statistically significant (P=0.86).<sup>2,14,15</sup>

**Investigation**

Although GBCs are generally more advanced at presentation than non-GBCs it is unlikely this is due to a differing behaviour of the disease. The main reason for worse outcomes in GBC has been reported to be due to delays in diagnosis. The likely reason for this delay is that abnormalities detected in the pregnant or lactating breast by the patient or clinician are thought to be due to hormonal changes and nothing more sinister. Overall, the literature demonstrates a delay in investigation of 2-15 months from the first appearance of symptoms to confirmed diagnosis in GBC than in their nonpregnant counterparts.<sup>2,3,5,6,12,15,16</sup> General practitioners can play an important role in the early detection of GBC by promoting breast awareness in their premenopausal patients and by prompt and appropriate referral of pregnant and lactating women with breast abnormalities.

Any breast abnormality found in a pregnant or lactating woman should be investigated, in the same way as the non-pregnant woman, by triple assessment - clinical assessment, imaging and tissue biopsy. The physiological changes in the pregnant or lactating breast may mask the appearance of a lump, but it is inappropriate to delay investigation on the basis that the abnormality may be related to pregnancy or lactation.<sup>1,17,18</sup> The differential diagnosis of breast symptoms in pregnancy are outlined in Table 1. Only breast lumps that are benign by all three arms of assessment, can be safely observed.

There are some difficulties with assessing the pregnant/lactating breast. Fine needle aspiration cytology is more difficult to interpret because of cellular changes within the pregnant or lactating breast.<sup>19</sup> Core biopsy may give more accurate information, but it is more invasive and there is a small risk of developing a milk fistula.<sup>20-22</sup> It is important for all clinicians to clearly specify on pathology requests that the woman is pregnant or lactating, to allow the most accurate appraisal of the specimen.

Medical imaging of the breast during pregnancy is safe as long as guidelines are followed. The exposure of the fetus to radiation should be minimised, and initial mammography is considered safe, if abdominal lead protection is used.<sup>21,23</sup> Mammography is not always diagnostic in young women because of the denseness of the breast tissue, and when pregnant or lactating this denseness is heightened.<sup>21,24,25</sup> With improved imaging quality and techniques this may become less of an issue in the future. Ultrasound may give equivalent information, or indeed more accurate information of the breast, with as yet no known ill effects to the fetus.<sup>21,23</sup>

Pathologically there are probably no discernable differences in tumour type between gestational and nongestational breast cancer. A large proportion of node positive GBCs are found at the time of surgery, with most series reporting approximately 70% as node positive -

**Table 2. Management of GBC**

- Multidisciplinary approach
- During pregnancy:
  - surgery, usually mastectomy recommended
  - radiotherapy contraindicated
  - chemotherapy, safe after the first trimester
  - hormone therapy contraindicated
- Postpartum:
  - normal management of breast cancer, with cessation of lactation

again an indication of late presentation.<sup>2,26,27</sup> Generally there are similar incidences of inflammatory cancers in both gestational and nongestational breast cancer with rates between 1.5-4.0%.<sup>11,22,28</sup>

Very little research has been carried out on the histological appearance of GBCs, but there appears to be no difference from those in non-GBC.<sup>29,30</sup> Larger studies need to be carried out to provide conclusive evidence of biological differences between gestational and nongestational cancers.

**Management**

Initial management of GBC is best accomplished in a tertiary referral centre where a multidisciplinary approach can be utilised (Table 2). This team should not only include those treating the breast cancer but those involved in the care of the pregnancy so that both mother and child have the best chance of survival. The preferred surgical treatment of breast cancer during pregnancy is mastectomy. Breast conserving surgery and postoperative radiotherapy, which is the routine treatment for breast cancer, is largely contraindicated during pregnancy. This is because radiotherapy to the breast, chest wall or axillary lymph nodes cannot safely be carried out during pregnancy.<sup>1</sup> When GBC is diagnosed in the third trimester then radiotherapy can be performed after the safe delivery of the child and in lactating women with lactation ceased before treatment.<sup>21</sup>

Chemotherapy administered during the

first trimester results in unacceptably high levels of fetal abnormality.<sup>131</sup> During the second and third trimester chemotherapy can safely be given (a malformation rate of 4% is reported - similar to the 3% risk during a normal pregnancy), although it may be associated with low birth weight and early delivery.<sup>32,33</sup> There are specific agents that should be avoided as treatment during pregnancy including antimetabolites such as methotrexate.<sup>34</sup> To date, long term follow up has demonstrated normal growth and development of children exposed to antineoplastic agents in utero. As yet no clear evidence has supported the concern of delayed malignancies or infertility developing in these children.

The question arises in GBC whether termination of pregnancy should be a management option. In the past, termination has been the only option given to some women, but there is no evidence to demonstrate a survival benefit. Some studies have shown that termination of pregnancy can make the breast cancer prognosis worse.<sup>10</sup> These results may however, be biased, as it is possible that women with more advanced disease or poorer prognostic features were recommended for termination of pregnancy, and these women would have a decreased chance of survival with or without termination.<sup>20,21</sup> In the 21st century when breast cancer can be managed safely during pregnancy, a women choosing to continue her concurrent pregnancy can do so with minimal concern for the child's wellbeing. As Byrd succinctly said in 1968: 'In the face of general enthusiasm for terminating the pregnancy, we believe the evidence is that the cancer should be terminated.'<sup>16</sup>

Termination of the pregnancy may be medically indicated in women who present with advanced breast cancer very early in the pregnancy when urgent treatment is required.<sup>4,21,35</sup> Ultimately women in this difficult situation, given adequate information and support, should be able to make their own informed choice about their breast cancer management and the outcome of their pregnancy.

### Subsequent pregnancy

Contraception and fertility are two important issues for premenopausal survivors of breast cancer. There are many ways these issues impact on a woman's life including the social, psychological, economic and biological aspects, especially when their lifespan is potentially limited.<sup>1</sup> These important issues require discussion, but are difficult for practitioners to discuss at the time of diagnosis, especially when there is little evidence on which to base choices.

Pregnancy is not recommended in the first two years following treatment.<sup>36,37</sup> This is mainly to ensure the patient does not develop early recurrence, with its poor prognosis. Therefore some form of contraception is likely to be necessary but many clinicians will discourage hormonal contraception. This is because oral contraceptive pill (OCP) users are known to have a small increased risk of developing breast cancer and at present the hormonal effect of OCP use on any residual tumour following breast cancer treatment is unknown.<sup>23,38</sup>

The decision to have a child, planned or otherwise, is difficult. Questions such as:

- 'what influence will the pregnancy have on the breast cancer'
- 'will my breast cancer recur', and
- 'what effect will the breast cancer and its treatment have on my child'

are likely to arise. Breast cancer survivors who subsequently conceive have equivalent survival, and in some studies better survival, matched for stage than those survivors who don't conceive.<sup>2,26,27,39-42</sup> This suggests that subsequent pregnancy may provide a survival benefit, but there may be bias involved, with only a select group of women, who are generally healthy going on to become pregnant - a 'healthy mother' effect.<sup>43</sup>

### Fertility

At the other end of the spectrum chemotherapy can reduce fertility. It has been estimated that only 7% of fertile women go on to conceive following a diagnosis of breast cancer.<sup>1,44,45</sup> Many women who have chemotherapy for breast cancer will become amenorrhoeic, especially those over 40 years of age.<sup>46</sup> In women with oestrogen receptor positive tumours, this may account for much of the beneficial effect of chemotherapy in breast cancer treatment.<sup>31</sup>

Infertility can be devastating for the woman who desperately wants a child. Various strategies have been proposed to protect the fertility of a woman undergoing chemotherapy. These include reversible chemical sterilisation to protect the follicles during therapy and cryopreservation of ovarian tissue but as yet there is no way to produce an embryo using this tissue.<sup>47</sup>

### Ongoing research in Australia

There is a project currently underway which will investigate breast cancer and pregnancy in the Western Australian population (Table 3). The WA Record Linkage System<sup>48</sup> will be used to identify women who were diagnosed with GBC or have survived breast cancer and subsequently conceived since 1982. Information will be gathered on diagnosis, treatment and outcomes of the breast cancer and pregnancy. We anticipate this study will lead to a greater understanding of breast cancer and pregnancy, and will allow the development of best practice guidelines on which medical practitioners can base their management of these groups of women. It will also provide information, which will enable women to make informed choices about their future.

**Table 3. Western Australian Project**

- Identify women aged 15-45, diagnosed with GBC since 1982
- Identify breast cancer survivors, aged 15-45, who have subsequently conceived since 1982
- Gather information on the investigations undertaken and the management and outcome of breast cancer and pregnancy

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