Royal College of Obstetricians and Gynaecologists

Setting standards to improve women's health

Guideline No. 12
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PREGNANCY AND BREAST CANCER

1. Introduction

Breast cancer remains the most common cancer in women, with a lifetime risk of almost 11% (one in nine) in the UK.[1] There has been an overall increase in the incidence of breast cancer but in the UK mortality has fallen by over 30% in the last decade. It is likely that this is due to the widespread introduction of tamoxifen in treatment regimens and the introduction of breast screening.[2]

Obstetricians will see an increasing number of women who are pregnant or seeking pregnancy after treatment for breast cancer. This guideline updates the RCOG advice published in July 1997.

2. Methodology

A literature search was performed using Medline (1997–2002). The key words used were 'breast cancer', 'breast neoplasms', 'mastectomy', 'pregnancy', 'pregnancy complications', 'breastfeeding', 'lactation', 'fertility', 'infertility', 'abortion', 'contraception', 'contraceptive devices' and 'contraceptive agents'. Abstracts were used to identify key articles.

The definitions of the types of evidence used in this guideline originate from the US Agency for Health Care Research and Quality. Where possible, recommendations are based on, and explicitly linked to, the evidence that supports them. Areas lacking evidence are highlighted and annotated as 'good practice points'.

3. Reproductive factors and breast cancer risk

Reproductive factors are strongly linked to subsequent risks of breast cancer. Nulliparity is associated with an increased risk and parity reduces the risk, although there is evidence that the risk of breast cancer is transiently increased after pregnancy. In a Swedish study,[3] women within three years of their last childbirth had an estimated risk of 1.21 (95% CI 1.02–1.44) compared with women whose last birth was ten or more years earlier, after adjusting for parity and age at first birth. A Norwegian study[4] observed a short-term increase in the risk of breast cancer after a full term pregnancy, with a maximum risk three to four years after delivery followed by a subsequent decrease in risk.

Evidence level III

Early menarche and late age at first pregnancy are associated with increased risk.[5] A pregnancy that ends with preterm delivery has less transient increased risk and less long-term protection.[6,7] The influence of hormonal factors in pregnancy is uncertain.[8–12]

Several epidemiological studies have shown that the risk of breast cancer is reduced if the pregnancy is complicated by an increase in blood pressure, pre-eclampsia (or toxaemia) or smaller placentas.[13–15]

Evidence level III

Pregnancy also increases the risk of breast cancer developing in carriers of *BRCA1* and *BRCA2* mutations.[16] Carriers of these mutations who have children are significantly more likely to develop breast cancer by the age of 40 years than carriers who are nulliparous, and each pregnancy is associated with an increased risk of cancer. Having a baby at a young age does not appear to protect *BRCA1/BRCA2* carriers against subsequent development of breast cancer.[17]

In a systematic review of 28 published studies, Lipworth *et al*.[18] concluded that breastfeeding conferred a weak protective effect on risk of breast cancer with longer duration of breastfeeding. Bernier,[19] in a meta-analysis of 23 published studies, also confirmed a slight but significant reduction in breast cancer in women who had breastfed, which appeared to be related to the duration of breastfeeding. The Collaborative Group on Hormonal Factors in Breast Cancer undertook a reanalysis of 47 previous studies.[20] After stratifying for other known risk factors they concluded that each year of breastfeeding confers a reduction of about 4.0% in breast cancer risk.

Evidence levels III and IV

Women should be advised to breastfeed if possible, as this is likely to reduce their risk of breast cancer in addition to any other benefit.

C

Although there has been controversy concerning breast cancer risk and termination of pregnancy, available evidence on an association between induced abortion and breast cancer is inconclusive.[21]

Evidence level III

4. Breast cancer during or soon after pregnancy

Only about 3% of women diagnosed with breast cancer will be pregnant. Unfortunately, when the diagnosis is made during or soon after pregnancy, the prognosis is worse, with an increased risk of late-stage disease, particularly if the woman is aged 30 years or less.[22–26]

Some of this poor prognosis is due to advanced stage at diagnosis (difficulty in detecting pathology within a breast with physiological changes of pregnancy) or delays with treatment.[27] Some have suggested that if survival is matched for grade and stage among nonpregnant controls then the survival is equivalent[28–30] but others have consistently found poor survival, even when adjusting for such factors.[31]

Evidence level III

5. Treatment of breast cancer during pregnancy

There is no evidence that termination of pregnancy after diagnosis of breast cancer is necessary to improve prognosis

Treatment during pregnancy will require discussion between the woman, the oncologist and the obstetrician on the relative benefits of early delivery followed by treatment versus commencement of therapy while continuing the pregnancy. Generally the data for immediate treatment are reassuring, and delay or refusal to undergo therapy has serious consequences.[27,32]

Although standard protocols are not available, surgery is usually the first-line treatment, with mastectomy or lumpectomy and axillary clearance being the preferred option and deferring reconstruction. In one case series, the majority of women (18 of 22) underwent modified radical mastectomy, followed by combination chemotherapy consisting of 5-fluorouracil, doxorubicin and cyclophosphamide.[33]

Evidence level III

Provided that chemotherapy is not used in the first trimester (when it may induce spontaneous miscarriage[34]), it appears to be relatively safe for subsequent use.[35] Although there is a general recommendation to avoid the use of tamoxifen during pregnancy,[36] there is a case report of its use during pregnancy with metastatic breast cancer.[37] The use of radiotherapy to treat breast cancer in pregnancy is not absolutely contraindicated but an appropriate thickness of lead shielding should be used to reduce fetal dose.[38,39]

Evidence level III

If chemotherapy is necessary in the first trimester, termination of pregnancy may be proposed. Bernik *et al*.[35] advise that, if the cancer is detected in the second trimester and is early-stage, lumpectomy can be followed by chemotherapy and radiation can be withheld until after the birth of the child. In the third trimester, if cancer is detected close to term, it may be possible to defer treatment for a short period and induce delivery.

Evidence level IV

6. Pregnancy after treatment of breast cancer

Women planning a pregnancy after treatment for breast cancer should consult their obstetrician, breast surgeon and clinical oncologist.

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6.1 Effects of treatment on fertility

It has been suggested that up to 7% of women who are fertile after treatment for breast cancer will subsequently have children.[40] Most young women will no longer undergo surgical or radiation ovarian ablation[41] but it is recognised that chemotherapy may cause premature ovarian failure, depending upon the woman's age and the treatment regimen. Cyclophosphamide, which is an alkylating agent, can damage resting cells, while methotrexate and fluorouracil (as combination CMF) are cell cycle-specific, i.e. they affect dividing cells. Bonadonna and Valgussa[42] reported that 96% of women over 40 years of age and receiving six or 12 cycles of CMF for breast cancer developed amenorrhoea after treatment, whereas 54% of women under 40 years experienced amenorrhoea that was reversible in 23%. Resumption of menstruation does not confirm restoration of fertility but was more likely in younger than older women.

The information about the effect of doxorubicin on fertility is limited but 9% of women younger than 35 years and receiving fluorouracil, doxorubicin and cyclophosphamide developed permanent amenorrhoea.[43] The taxanes, paclitaxel and docetaxel, are used in treating breast cancer but there is not yet sufficient information to assess their impact on fertility.[44]

Evidence level III

To date, there is no evidence that any of these cytotoxic drugs used prior to a pregnancy produce any adverse effects on fetal development or the neonate.

It seems that pregnancy after treatment for breast cancer has an increased chance of spontaneous pregnancy loss.[45]

6.2 Risk of recurrence

Long-term survival after breast cancer does not appear to be affected by pregnancy.

C

Generally, the prognosis is good for women with a subsequent pregnancy after early-stage cancer,[45–47] with evidence of a 'healthy mother effect'.[48] Among 41 women observed over 30 years at Memorial Sloan Kettering Cancer Centre there was a five-year survival rate of 80%.[49] In a nationwide French study, the ten-year survival rate of 68 women who had subsequent pregnancies

Evidence level III (Ca153 is level IV)

was 71%.[50] The survival of women who were node-negative was 90% at ten years and there was no difference between those who had subsequent pregnancies and those who did not. In another study, the ten-year survival was 56% among 16 women with node-positive disease and 55% for women who did not become pregnant.[51] It has been suggested that serum CA153 may be a useful marker for monitoring pregnant women with breast cancer.[52]

Evidence level III (Ca153 is level IV)

6.3 Interval before attempting conception

It is recommended that pregnancy should be deferred for at least two years after treatment. **C**

Several authors have recommended that pregnancy should be delayed for at least two years after breast cancer treatment.[53,54] It is likely that this timescale helps to differentiate those with a better chance of long-term survival from those with more aggressive disease. A five-year survival of 54% has been reported for women with an interval to pregnancy of less than six months, compared with 78% from six months to two years, and 100% for those women who waited for more than five years.[55] As younger women have significantly lower survival rates and higher local and distant relapse rates than older women, those under 33 years of age might be better advised to delay pregnancy for at least three years, to reduce the risk of relapse.[56]

Evidence level III

Averette *et al*.[57] have recommended that decisions about future conception should be based on the prognosis for the individual woman. They advise that women with stage-IV disease (with a five-year survival of less than 15%) should not consider a pregnancy and that women with stage-III disease should consider deferring pregnancy for at least five years after treatment. Women with recurrent stage-I or -II tumours should not contemplate conception because of the intensity of the required treatment and the poor prognosis.

Evidence level IV

6.4 Fertility treatment

There is no current information about the influence of ovarian stimulation on the risk of recurrence in women who have completed treatment for breast cancer.

Increasing numbers of women wish to consider fertility preservation prior to chemotherapy. Embryo freezing is well validated[58] but only suitable for women with a partner. Egg freezing and ovarian tissue cryopreservation are not yet well established and women should be counselled as to the limited success of these approaches. High levels of circulating oestrogen during ovarian stimulation might have an adverse effect on oestrogen-sensitive tumours and this should be considered when counselling oestrogen-receptor positive women prior to chemotherapy.

7. Breastfeeding

There is no evidence that women who have completed treatment for breast cancer cannot breastfeed safely from the unaffected breast. Breast-conserving surgery may not inhibit lactation but radiotherapy causes fibrosis and lactation is unlikely in an irradiated breast. During treatment for breast cancer with chemotherapy or radiotherapy, women should not breastfeed.

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APPENDIX

Clinical guidelines are: 'systematically developed statements which assist clinicians and patients in making decisions about appropriate treatment for specific conditions'. Each guideline is systematically developed using a standardised methodology. Exact details of this process can be found in Clinical Governance Advice No. 1: *Guidance for the Development of RCOG Green-top Guidelines* (available on the RCOG website at www.rcog.org.uk/clingov1). These recommendations are not intended to dictate an exclusive course of management or treatment. They must be evaluated with reference to individual patient needs, resources and limitations unique to the institution and variations in local populations. It is hoped that this process of local ownership will help to incorporate these guidelines into routine practice. Attention is drawn to areas of clinical uncertainty where further research may be indicated.

The evidence used in this guideline was graded using the scheme below and the recommendations formulated in a similar fashion with a standardised grading scheme.

Classification of evidence levels

Ia	Evidence obtained from meta-analysis of randomised controlled trials.
Ib	Evidence obtained from at least one randomised controlled trial.
IIa	Evidence obtained from at least one well-designed controlled study without randomisation.
IIb	Evidence obtained from at least one other type of well-designed quasi-experimental study.
III	vidence obtained from well-designed non-experimental descriptive studies, such as comparative studies, correlation studies and case studies.
IV	Evidence obtained from expert committee reports or opinions and/or clinical experience of respected authorities.

Grades of recommendations

A	Requires at least one randomised controlled trial as part of a body of literature of overall good quality and consistency addressing the specific recommendation. (Evidence levels Ia, Ib)
B	Requires the availability of well controlled clinical studies but no randomised clinical trials on the topic of recommendations. (Evidence levels IIa, IIb, III)
C	Requires evidence obtained from expert committee reports or opinions and/or clinical experiences of respected authorities. Indicates an absence of directly applicable clinical studies of good quality. (Evidence level IV)

Good practice point

✓	Recommended best practice based on the clinical experience of the guideline development group.

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The final version is the responsibility of the Guidelines and Audit Committee of the RCOG.

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