Dilemma of Pregnant Ladies with Breast Cancer

Zainur Rashid Z[1], S Sulaiha S A[1], Lew K G[2], Nurhana S[2]

Gestational breast cancer (GBC) or pregnancy-associated breast cancer was defined as breast cancer diagnosed during pregnancy and within 1 year of delivery. Breast cancer is the second commonest cancer after cervical seen in pregnancy and lactation. Nevertheless, the incidence is low and accounts for approximately 1 in 3000 of pregnancies. A delay in diagnosis is common and 70% to 89% of patients with operable primary lesions already have positive axillary lymph nodes. Breast cancer identified during pregnancy can be extremely distressing for the mother despite it has similar course of disease and prognosis seen in non-pregnant women of the same age and stage of disease. Diagnostic and treatment options should be carefully decided to prevent further harm to the mother or any potential risk to the developing fetus.

IeJSME 2009: 3 (2): 3-7

Key words: Breast cancer; Pregnancy; Diagnosis; Management

Women undergo hormonal level changes during pregnancy and this has resulted in changes of the breast (i.e. breast volume and firmness). Hormonal factors, especially oestrogen appear to play an important role early on in the development of breast cancer.[1] However, pregnancy itself has not clearly shown to influence the outcome of an established breast cancer.

Breast cancer is one of the commonest malignancies identified during pregnancy and lactation, affecting approximately 0.03% of pregnancies.[2] The average age of patient is between 32 to 38 years of age. It has been shown that the incidence of breast cancer may increase as more women choose to delay childbearing.[3] Delays in diagnoses are common, with an average reported delay of 5 to 15 months from the onset of symptoms due to the natural tenderness and engorgement of the breasts of pregnant and lactating women. In a study conducted by Nettleton J et al., a 1-month delay in primary tumour treatment increases the risk of axillary metastases by 0.9%, and a 6-month delay increases the risk by 5.1%.[4]

Breast cancer in the child bearing age is no longer uncommon in Malaysia although the exact prevalence is unknown:

- It is the most common cancer among women above 20 years old in Malaysia.[5]
- The peak age group is 40 – 49 years old.[5]
- About 1 in 19 women have the chance of getting breast cancer.[5,6]
- 1 in 14 for Chinese
- 1 in 15 for Indians
- 1 in 24 for Malays

Although early detection is nowadays possible due to the increasing awareness and health consciousness especially during pregnancy, the management of breast cancer in pregnancy remains difficult and needs individualization.

Risk Factors

Risk factors for breast cancer includes carrier of BRCA I and BRCA II gene, women who are exposed to higher level of oestrogen for a longer period of time (early menarche and late menopause), nulliparity, did not breastfeed, history of benign breast lump, obesity, exposure to radiation, high fat diet and hormone replacement therapy.[7]

The relative risk of getting breast cancer however is not known to increase during pregnancy. The overall risk of breast cancer in fact reduces during pregnancy. After pregnancy, the risk temporarily rises and is usually higher in women with positive family history of breast cancer. In a woman without family history, U-shaped pattern of relative risk is observed after pregnancy. For women with first degree family history, pregnancy did not have any effect on the risk of getting breast cancer.[8] The survival rate for the mother diagnosed shortly after pregnancy is poorer than the prognosis in those who are diagnosed later.

Nevertheless, women with gestational diabetes mellitus are said to have one and a half times greater risk

[1]Department of Obstetrics & Gynaecology, International Medical University, MALAYSIA
[2]Research Students, International Medical University, MALAYSIA

Address of Correspondence:
Assoc Prof Dr Zainur Rashid Bin Zainuddin, Department of Obstetrics & Gynaecology, International Medical University Clinical School, Jalan Rasah, 70300 Seremban, Negeri Sembilan, MALAYSIA
Tel: 606-7677798 Fax: 606-7677709 Email: zainurrashid_zainuddin@imu.edu.my

of getting breast cancer if compared with women who did not have diabetes mellitus.[9] Lower risk of breast cancer is on the other hand observed in women who have pregnancy related hypertension such as preeclampsia.[10] In a study conducted by Inners and Byers, women who develop pre-eclampsia tend to have higher levels of androgens, lower oestrogen and progesterone levels than women in normotensive pregnancies.[11] Low oestrogen level reduces the chance of getting breast cancer.

Table 1: Risk Factors to breast cancer

NON PREGNANT LADIES	PREGNANT LADIES
Early menarche & Late menopause	
Nulliparous	Diabetes in pregnancy
Did not breastfeed	After pregnancy
History of having benign breast lump	Family history of breast ca
Obesity	*Hypertension in pregnancy
High Fat diet	
Hormone Replacement therapy	
Exposure to radiation	
Family history of breast ca	

**Reduces risk of breast Ca in pregnancy*

Diagnosis

Pregnant and lactating women should practice self breast examination as part of routine prenatal examination in order to detect breast cancer.[12] Clinicians should always investigate a breast abnormality using triple assessment – clinical assessment, imaging and tissue biopsy even in pregnant or lactating women.

Ultrasound and mammography may be used to locate occult carcinoma if an abnormality is found (i.e. presence of suspicious physical findings).

Many is sceptical when performing mammogram in a pregnant woman due to its use of radioactive ray even though it is non invasive. However, mammography only poses little risks of radiation to the fetus during pregnancy if a lead shield is placed on the belly to block any possible radiation scatter.[13] Nevertheless, its false negative is found worrying. This could probably be caused by increased breast density, vascularity and water content during pregnancy.[14] In a study conducted by Yang WT et al., at least 25% of mammograms in pregnancy may show negative results despite the presence of cancer.[13] Ishida et al, found merely 34 of 50 mammograms successfully diagnose carcinoma.[14] A few other studies also reported similar findings with mammogram.[15,16] Therefore, a biopsy is essential to confirm diagnosis of any palpable mass detected during pregnancy.

Breast ultrasonography in pregnancy is also useful in distinguishing between a cystic or solid mass. However, it is not possible to distinguish benign from malignant solid masses. Furthermore, little is known about the ultrasonography appearance of normal breasts during pregnancy. This technique detected 39 of 42 cancers (~93%) in a case-control study of pregnant Japanese women and detected all pregnancy-associated tumours in another two small series.[16] However, 2 of the 4 malignant tumours in 1 of those series appeared benign on ultrasound.[17]

Magnetic resonance imaging (MRI) is another useful non invasive tool used in pregnancy or during lactation. However, there is no data or studies available on its affect if used on pregnant women. It is said to have minimal exposure of ionizing radiation to the fetus but is associated with risks of heating and cavitation thus its safety of use in pregnancy is questionable. Generally, it is preferred only in the case of metastases.[16]

Diagnosis may be safely accomplished with biopsies, which is the gold standard for the diagnosis of breast cancer. Alternatively, fine-needle aspiration may be used. In 2 small series, fine-needle aspiration detected all cancers in pregnancy. However, 1 patient in each study, the results were initially categorized as atypical rather than an indication of carcinoma.[18-21]

Table 2: Suitable Diagnostic tests for Pregnant Ladies

Biopsies :- FNAC, Tissue Biopsy	+++++
Magnetic Resonance Imaging	+++
Breast Ultrasound	++
Mammography	++

Treatment

The treatment goal for breast cancer in a pregnant woman is similar as for a non-pregnant woman which is to achieve local and systemic control of the disease. However, for pregnant woman, the impact of the treatment towards the fetus and effect of possibly delaying therapy have to be considered.

The treatment option will depend on type and size, location, stage of the tumour and stage of the pregnancy. The options of management will include removal of the lump; either it is lumpectomy or mastectomy, radiotherapy and chemotherapy. The course of management will depend on the stage of the cancer.[22] On the other hand, treatment options in pregnancy will be limited since some treatment is thought to increase the risk for fetal malformations or stillbirth.

Surgery will be the first line treatment for non-metastasize breast cancer. There is no known evidence that surgical procedure will be risky to the fetus as only 1% risk of spontaneous abortion is recorded in mastectomy.[23] However, radiotherapy will not be started until the baby is born.

Radiotherapy is used usually after surgical removal of cancerous masses to decrease recurrence of breast cancer but the high doses of radiation can be teratogenic to the fetus especially in the first trimester; therefore, it is usually deferred during pregnancy.[23]

Early Stage Breast Cancer (Stage 1 & 2)

Recommended primary treatment for breast cancer diagnosed in pregnancy is surgical treatment. Modified radical mastectomy will be the treatment of choice since this will not expose the fetus to harmful scattered radiation. However, for breast preservation, conservative surgery with postpartum radiation is used.

Chemotherapy might be used as an adjuvant treatment after the surgery. However, it should be avoided during the first trimester of pregnancy as some might have teratogenic effect.[21] Adjuvant chemotherapy given during second and third trimester will not increase the risk of birth defect or stillbirth.

Adjuvant chemotherapy may also be delayed until after the baby is born if the cancer is diagnosed during the third trimester. Birth may be induced in certain cases.[23] However, one study in women receiving fluorouracil, doxorubicin, and cyclophosphamide within 10 weeks or after 10 weeks of surgery for breast cancer shows that there is no increase in disease-free survival.[24] However, chemotherapy can lower the mother's blood count, and this can cause bleeding and increase chance of infection during birth if it is given 3 to 4 weeks before delivery.

Late Stage Breast Cancer (Stage 3 & 4)

Radiation therapy should be avoided if the mother is in the first trimester of pregnancy. Chemotherapy may be given to the mother. However, discussion whether the pregnancy should be terminated or not should be done with the mother as there is high risk of fetal damage.

Table 3: Therapeutic options according to gestational age of pregnancy

OPTIONS	1ST TRIMESTER	2ND TRIMESTER	3RD TRIMESTER
Surgery – mastectomy	Strongly recommended	Strongly recommended	Strongly recommended
Chemotherapy	Deferred due to teratogenicity	May be given	May be given
Radiotherapy	Not recommended	Not recommended	Not recommended

Termination of Pregnancy

In a study conducted by Petrek et al., termination of pregnancy has not been shown to have any beneficial effect on breast cancer outcome and is not usually considered as a therapeutic option.[25] However, it may be considered based on the age of the fetus and if maternal treatment options, such as chemotherapy and radiation therapy are significantly limited by the continuation of the pregnancy. Furthermore, termination of pregnancy does not appear to improve survival.[26] Hence, decisions regarding termination of pregnancy should be based on the desires of the patient, along with the urgency for radiation or chemotherapy that could potentially be harmful to the fetus.

Generally, termination of pregnancy is advised if the breast cancer is discovered in early pregnancy and then the breast cancer is treated accordingly. However, if the disease is noticed in late pregnancy, mothers can choose to wait until fetal viability and then deliver the baby via lower segment caesarean section (LSCS) followed by the treatment for breast cancer as stated above.

Prognosis

Patients with breast cancer during pregnancy have the same prognosis as non pregnant patients if matched for age and stage of disease. The mortality rate of breast cancer during pregnancy is significantly affected by its delay in presentation.[26, 27]

Women who are diagnosed as having breast cancer during pregnancy will have 2.5 times increase risk of having metastasis if compared to non-pregnant women.[27] This could be caused by a delay in diagnosis or due to increased vascularity of the breast as the pregnancy advances.

The disease stage at diagnosis is the most important predictor of survival. Pregnancy following the diagnosis of breast cancer does not have a known detrimental effect on survival, although it is usually wise to discourage pregnancy for the first few years following the diagnosis of breast cancer and treatment.[28]

Breastfeeding

It is said that breastfeeding is a protective factor to breast cancer. The longer women breast feed the more they are protected against it.[29] However, in the event where diagnosis has been achieved, she should stop breastfeeding if planned to undergo any surgery or chemotherapy. It will also reduce blood flow to the breast, thus decreasing the risk of any complication (i.e. excessive haemorrhage) during the surgery. Some chemotherapy drugs might be passed on to the baby through breast milk. Therefore, it is also contraindicated during breastfeeding.

Conclusion

Breast cancer is a rare medical problem during pregnancy. The incidence of breast cancer during pregnancy is likely to increase as more women delay child-bearing. Mammograms and breast ultrasound were found to be useful in diagnosing breast cancer in pregnant women. A multidisciplinary approach consisting of surgeons, oncologist, obstetrician and paediatrician is necessary to decide the best treatment for both mother and baby without compromising their health. Counselling to the patient is also important prior to any decision-making to suit each patient's desire. Combination chemotherapy with FAC (5-flurouracil, adriamycin and cyclophosphamide) has been safely administered to women in the second and third trimesters, with minimal complications to mother and fetus.

Key Points

~ Pregnant women with breast cancer have a similar prognosis to that of non-pregnant women with the disease.

~ However, pregnant women tend to be diagnosed later than non-pregnant women and this leads to poorer prognosis and higher rate of metastasis.

~ Surgical treatment is the treatment of choice in breast cancer during pregnancy.

~ Radiation therapy should be avoided in the first trimester to avoid the risk of fetal malformation or stillbirth.

~ Termination of pregnancy is not indicated and will not improve the prognosis, but can be considered in the first trimester to prevent delay of treatment.

~ Breastfeeding should be stopped if surgery is planned to prevent complication.

~ Breastfeeding during chemotherapy is contraindicated as some of the drugs might pass through breast milk.

~ Pregnancy after breast cancer does not alter the outcome of treatment

~ The ideal interval between treatment for breast cancer and subsequent pregnancy is unclear

REFERENCES

1. Moore HC, Foster RS Jr. Breast cancer and pregnancy. Semin Oncol 2000, 27: 646-53.
2. Donegan WL. Breast carcinoma and pregnancy. In Donegan WL, Spratt JS (eds): Cancer of the Breast. 4th Ed. Philadelphia: WB Saunders 1995; 732-41.
3. Chie WC, Hsieh CC et al. Age at Any Full-term Pregnancy and Breast Cancer Risk. Am J Epidemiol 2000; 151: 715-22.
4. Nettleton J, Long J, Kuban D, Wu R, Shaeffer J, El-Mahdi A. Breast cancer during pregnancy: quantifying the risk of treatment delay. Obstet Gynecol 1996; 87: 414-8.
5. Noor Hisham A, Yip CH. Spectrum of Breast Cancer in Malaysian Women: Overview. World J Surg 2003; 27: 921-3.
6. The second report of The National Cancer Registry – Cancer Incidence in Malaysia 2003.
7. Rubin E. Carcinoma of the Breast. Essential Pathology. Lippincott Williams & Wilkins 3rd Edition 2001; 542-44.
8. Hemminki K, Forsti A, Sundquist J, Ji J. Risk of familial breast cancer is not increased after pregnancy. Breast Cancer Res Treat 2008; 108: 417-20.
9. Perrin MC, Terry MB, Kleinhaus K et al. Gestational diabetes and the risk of breast cancer among women in the Jerusalem Perinatal Study. Breast Cancer Res Treat 2008; 108: 129-35.
10. Terry MB, Perrin MC, Carolyn M et al. Preeclampsia, Pregnancy-related Hypertension, and Breast Cancer Risk. Am J of Epidemiol 2007; 165: 9.
11. Innes KE, Byers TE. Pre-eclampsia and breast cancer risk. Epidemiology 1999; 10: 722-32.
12. Pelsang R. Diagnostic imaging modalities during pregnancy. Obstet Gynecol Cli North Am 1998; 25: 287-300.
13. Yang WT, Dryden MJ, Gwyn K, et al.: Imaging of breast cancer diagnosed and treated with chemotherapy during pregnancy. Radiology 2006; 239: 52-60.
14. Ishida T, Yokoe T, Kasumi F, et al. Clinicopathological characteristics and prognosis of breast cancer patients associated with pregnancy and lactation: analysis of case-control study in Japan. Jpn J Cancer Res 1992; 83: 1143-9.
15. Max MH, Klamer TW. Pregnancy and breast cancer. South Med J 1983; 76: 1088-90.
16. Samuels T, Liu F-F, Yaffe M, Haider M. Gestational breast cancer. Can Assoc Radiol J 1998; 49: 172-80.
17. Garel C, Brisse H, Sebag G, Elmaleh M, Oury J, Hassan M. Magnetic resonance imaging of the fetus. Pediatr Radiol 1998; 28: 201-11.
18. Westenend PJ, Sever AR, Beekman-De Volder HJ, Liem SJ. A comparison of aspiration cytology and core needle biopsy in the evaluation of breast lesions. Cancer 2001; 93: 146-50.
19. Shannon J, Douglas-Jones AG, Dallimore NS. Conversion to core biopsy in preoperative diagnosis of breast lesions: is it justified by results? J Clin Pathol 2001; 54: 762-5.
20. Poniecka AW, Krasuski P, Gal E, Lubin J, Howard L, Poppiti RJ. Granulomatous inflammation of the breast in a pregnant woman: report of a case with fine needle aspiration diagnosis. Acta Cytol 2001; 45: 797-801.
21. Brenner RJ, Bassett LW, Fajardo LL, et al. Stereotactic core-needle breast biopsy: a multi-institutional prospective trial. Radiology 2001; 218: 866-72.
22. L. Barthelmes; LA Davidson, C Gaffney, CA Gateley; Pregnancy and Breast Cancer. BMJ 2005; 330: 1375-8.
23. William L. Donegan; Cancer and Pregnancy; CA Cancer J Clin 1983; 33:194-214.
24. Ludger Barthelmes, Louise A Davidson, Christopher Gaffney and Christopher A Gateley; Pregnancy and breast cancer. BMJ 2005; 330:1375-8.
25. Alistair E. Ring, Ian E. Smith, Alison Jones, Catherine Shannon, Eleni Galani, Paul A. Ellis; Chemotherapy for Breast Cancer During Pregnancy: An 18-Year Experience From Five London Teaching Hospitals. Journal of Clinical Oncology 2005; 23: 4192-97.
26. Petrek JA, Dukoff R, Rogatko A: Prognosis of pregnancy-associated breast cancer. Cancer 1991; 67: 869-72.
27. Gallenberg MM, Loprinzi CL: Breast cancer and pregnancy. Semin Oncol 1989; 16: 369-76.
28. Guinee VF, Olsson H, Moller T, Hess KR, Taylor SH, Fahey T, et al. Effect of pregnancy on prognosis for young women with breast cancer. Lancet 1994; 343: 1587-9.
29. Breast cancer and breastfeeding: collaborative reanalysis of individual data from 47 epidemiological studies in 30 countries, including 50302 women with breast cancer and 96973 women without the disease. Collaborative Group on Hormonal Factors in Breast Cancer. Lancet 2002; 360(9328):187-95.