Breast cancer during pregnancy

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Summary
Breast cancer is the most common cancer during pregnancy, with an average of one case per 3000 pregnancies\(^{(1,2)}\). It has been estimated that up to 3% of breast cancer occur during pregnancy, almost 80% of all breast lumps during pregnancy are benign\(^{(3)}\). Surgical treatment can be done safely during all trimesters of pregnancy\(^{(4)}\). Chemotherapy is contraindicated during the first trimester of pregnancy, due to its teratogenic effects, but can be given safely during the second and third trimesters. Delivery shouldn’t be induced before the 37th weeks\(^{(5)}\).

Diagnosis
The physiological changes which occur during pregnancy in the breast may delay diagnosis, as small lumps may be difficult to detect. The diagnosis, like in non-pregnant women, is based on the triad of clinical assessment, imaging (US and mammography with good shielding), and tissue biopsy (Trucut)\(^{(6)}\). Clinical examination of the breast during antenatal care should be a routine. Mammography can be done during pregnancy, experts agree that mediolateral views with adequate shielding to maintain fetal dose below the permissible radiation dose can be performed, but due to the increased density and vascularity of the breasts during pregnancy interpretation may be difficult\(^{(7)}\). With proper shielding the estimated dose of radiation of 2 views is 200-400 mCgy, and a sensitivity of 78 - 90% was reported\(^{(4)}\). However, US is more accessible, very useful and has high sensitivity and specificity and can differentiate between solid and cystic masses\(^{(8,9)}\). Trucut biopsy offers a reliable diagnostic tool with a sensitivity around 90%, and an extra benefit of receptors assay unlike Fine Needle Aspiration which may be misleading during pregnancy. The predominant type of breast cancer during pregnancy is invasive ductal cancer as in non pregnant women\(^{(10,11)}\).

Keywords: Breast cancer, pregnancy, chemotherapy

Staging
Ultrasound examination of the breast, axilla and abdomen is safe and informative during pregnancy. A chest X-ray with abdominal shield can be done safely during pregnancy, the expected fetal exposure ranges between 0-0.0001 Gy\(^{(12)}\). There is still controversy about the use of MRI during pregnancy; it can be used if the examination provides important information that would otherwise require
exposure to ionizing radiation. Its safety in the prenatal period have not been fully determined, so it should be used with caution specially during the first trimester of pregnancy.(13).

**Surgery**

Sentinel node biopsy (SNB) using 99m Technitium sulphur colloid is safe during pregnancy in early stages of breast cancer and the radiation dose is well below the minimum dose associated with adverse fetal effects(14,15). However, isosulfan shouldn’t be used during pregnancy, as it can cause serious anaphylactic reaction that can harm both the mother and the fetus(16).

Breast cancer surgery follows the same guidelines as in non-pregnant women and can be performed safely, with minimum risk to the fetus during the third-trimester of pregnancy, both breast conservative surgery (BCS) and modified radical mastectomies (MRM) can be done(17). As for reconstruction, there is data supporting the use of tissue expanders for reconstruction following mastectomy during pregnancy(18); however, some experts advice that it should be done after delivery(19). For management of the axilla, US guided needle biopsy of suspicious nodes is helpful. There is no evidence that the lymphatic drainage is altered by pregnancy, and axillary clearance is safe during pregnancy.

**Radiotherapy**

There is a controversy regarding the use of radiotherapy during pregnancy, its delay may increase the risk of local recurrence. Fetal exposure depends on fetal age, field size, dose and distance from the gravid uterus. Successful birth of healthy infants after radiotherapy during pregnancy were reported(20). So radiotherapy during pregnancy is possible with fetal dose below the deterministic threshold. During the first and second trimesters, the fetal dose is considerably below the threshold values associated with adverse fetal defects. During the third-trimester the dose exceeds this threshold. However, increased incidence of fetal malformation and mental retardation was reported with doses exceeding 100-200 mcg, so radiotherapy should be avoided during the third-trimester and should be postponed to after delivery(21,22).

**Systemic Treatment**

Chemotherapy is contraindicated during the first trimester of pregnancy as it increases the risk of spontaneous abortions and major malformations, especially during the first 8 weeks of gestation when most organogenesis occur. It can be given safely during the second and third trimesters after the 14th weeks(23,24). It is known that many cytotoxic drugs cross the placenta and so increase the risk of intrauterine fetal growth retardation and the risk of low birth weight(25). If breast cancer is diagnosed during the late third-trimester chemotherapy could be given after delivery(26). The commonest combination used is cyclophosphamide, a driamycine and 5 fluorouracil. Epirubicine can also be used instead of a driamycine(27). There is no enough data for routine use of taxanes during pregnancy; however, there is recent data which suggest that they can be used safely(28,29), evidence regarding fetal tolerance to taxanes is accumulating. Amant et al, in a collaborative study of 169 women who received taxanes during pregnancy reported no increase in the incidence of malformations(30). In HER2-positive breast cancer during pregnancy trastuzumab (Herceptin), a drug that increases the disease free survival and overall survival significantly, should be avoided during pregnancy. It causes oligohydramnios and anhydramnious(31,32). Chemotherapy should not be given3-4 weeks before delivery to avoid wound healing delay and hemorrhage(33). Tamoxifen hormonal therapy is not indicted during pregnancy as it increases the risk of congenital abnormalities by 20%, like birth defects, goldenhar syndrome and ambiguous genitalia(34,35,36). There is a concern about fetal CNS continuous growth through the three trimesters of pregnancy and exposure to chemotherapy. However, in Aviles et al, studied 48 children who were exposed to chemotherapy during pregnancy and reported no increased risk in neurological complications, congenital...
abnormalities, fetal or cardiac complications or malignancies\(^{(37)}\).

**Prognosis**

Considerable controversy exists regarding the influence of pregnancy on prognosis. Some studies didn’t confirm any negative effect of pregnancy on the prognosis\(^{(38)}\). The prognosis of breast cancer during pregnancy stage for stage is similar to their non pregnant counterparts\(^{(26)}\). Stensein et al reported no increased risk of cancer related deaths in breast cancer during pregnancy\(^{(39)}\). Studies have shown that there is no survival benefit from termination of pregnancy; however, in women with advanced stages or very aggressive disease the couple should be counseled regarding prognosis and the possibility of termination\(^{(26,40)}\).

**Prenatal and long-term follow-up**

Following chemotherapy, low birth weight due to premature labor or intrauterine fetal growth retardation was reported\(^{(41)}\). A meta-analysis had shown that the use of chemotherapy during the second and third trimesters is not associated with increased risk of congenital abnormalities\(^{(42)}\). Limited data is available regarding long term CNS problems of the children exposed to chemotherapy during the second and third trimesters. Aviles studied 84 children and found no increase in congenital cardiac, neurological or psychological side effects\(^{(37)}\). It is important that the fetus should be monitored and assessed by US before chemotherapy and before each cycle, timing of delivery depends on fetal maturation, disease stage and patient condition. Premature labor should be avoided before 35 weeks of pregnancy. The place and the mode of delivery should be decided by the obstetrician, although placental metastases is rare but the placenta should be examined\(^{(43)}\).

**Lactation and fertility**

Women should be informed that chemotherapy can cause premature menopause, and that they shouldn’t breast feed during chemotherapy or tamoxifen treatment. Recurrences and metastases usually occur during 2-3 years after treatment, so patients should be counseled and informed in case they are planning for another pregnancy\(^{(44)}\).

A meta-analysis of 14 studies, 1,244 cases and 18,145 controls confirmed that pregnancy in women with history of breast cancer is safe and doesn’t compromise overall survival\(^{(45)}\). But before attempting pregnancy a woman should be carefully assessed and counseled by her obstetrician and oncologist.

**References:**