The Mutual Relationship between Pregnancy & Breast Cancer

Essay

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Abstract

The diagnosis of breast cancer is difficult in pregnancy because of the physiological modifications of the breast in pregnancy. Although treatment modalities and timing should be individualized, both obstetricians and oncologists should offer at the same time optimal maternal therapy and fetal well-being.

The diagnosis can often be made with ultrasound alone, which should be the first choice as imaging procedure in the presence of a lump. In fact, ultrasound is highly diagnostic in patients with a dense pattern of the breast, as usually happens in young women. Second, the presence of the fetus dictates that the use of ionizing radiation should be limited as much as possible. Therefore, in the presence of a lump, which cannot be diagnosed as certainly benign by ultrasound, histopathologic diagnosis must be performed.

Most routine modes for tissue sampling, including open biopsies under local anesthesia, can be safely performed during pregnancy without harming the mother or fetus.

Surgery is usually the first treatment considered for patients with breast cancer. In women who are pregnant general anesthesia is complicated because of increased blood volume and coagulability, decreased lung capacity, slow gastric emptying and supine positional hypotension.

Surgery is safe at any time**,** but breast conservation performed during the first trimester is probably associated with an excessively long delay in postoperative radiotherapy. Therefore, in a patient at the first trimester who wants to continue the pregnancy and also wishes to conserve the breast all these issues have to be carefully discussed, and the patient has to be informed that a possible increased risk of local recurrence should be considered, even though this is difficult to quantify because of the lack of data. SLNB can be safely performed during pregnancy, without any significant risks to the fetus at any phase of pregnancy.

The timing of chemotherapy is crucial: While it is obviously preferable to postpone chemotherapy until after delivery, this is not always possible. For instance, locally advanced tumors may need to be treated in a neoadjuvant manner. In addition, for patients whose tumors do not express estrogen receptors, a late start of chemotherapy, that is >3

weeks after surgery, may worsen the prognosis dramatically as compared to an early start of chemotherapy**.** The efficacy of very late adjuvant chemotherapies, for example, starting later than 8 weeks after surgery, is unknown; thus chemotherapy may need to be started during pregnancy even in patients with estrogen receptor-positive tumors.

Chemotherapy is contraindicated in the first trimester of pregnancy as the fetus is undergoing organogenesis and is vulnerable to the teratogenic effects of chemotherapy. If chemotherapy cannot be postponed to the second trimester of pregnancy, abortion is indicated. In the second and third trimester, the use of chemotherapy does not seem to increase the risk of fetal malformations. The choice of chemotherapeutic medication remains difficult regarding the scarcity of information on the children's long-term outcome, leaving the treating physician in the ethical conflict to take care of an adequate cancer therapy but to protect the unborn from a potentially harmful treatment

Adjuvant therapy with tamoxifen should be started after pregnancy. the efficacy of aromatase inhibitors in premenopausal women is unproven, and the use of such agents during pregnancy is discouraged.

Adjuvant radiation therapy exposes the fetus to ionizing radiation, the start of adjuvant radiation therapy is never urgent; delays of radiation therapy of up to 3–4 months result in outcomes similar to those with earlier initiation**.** In most cases, therefore, the initiation of radiation therapy can be safely delayed until after delivery.

Cytotoxic chemotherapy may result in amenorrhea due to direct ovarian damage, either at the time of chemotherapy, with an immediate, irreversible menopause or subsequently some years after chemotherapy, during which oligomenorrhoea is noted. Women may become infertile either with oligomenorrhoea or with actual menopause.

One of the major concerns of patients who receive adjuvant chemotherapy or hormonal therapy after surgery for breast cancer is the potential delayed teratogenicity of such treatments. the practical advice is to wait at least 6 months from the end of chemotherapy & 3–6 months after tamoxifen withdrawal before attempting conception, to be sure that any damaged oocyte will be replaced by a normal one.

No reports specifically address the safety of breast-feeding in women who become pregnant after breast cancer, the safety and feasibility of breast-feeding after breast cancer remains an open issue.

The options for protecting fertility in women about to undergo treatment for breast cancer include the possibility of using Lutinizing hormone-releasing hormone (LHRH) agonist to protect the ovaries, embryo cryopreservation and either oocyte cryopreservation or ovarian tissue banking.

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Contents

List of Abbreviations

BCdP	Breast Cancer during Pregnancy
bFGF	basic Fibroblastic Growth Factor
BMI	Body Mass Index
CI	Confidence Interval
CMF	Cyclophosphamide/Methotrexate/Flurouracil
CNS	Central Nervous System
CPR	Cancer Pathology Registry
DCIS	Ductal Carcinoma Insitu
EBCTCG	Early Breast Cancer Trialists, Collaborative Group
EGF	Epidermal Growth Factor
ER	Estrogen Receptor
FAC	Flurouracil /Adriamycin/ Cyclophosphamide
FEC	Flurouracil /Epirubicin/ Cyclophosphamide
FNA	Fine Needle Aspiration
FSH	Follicle Stimulating Hormone
GCSF	Granulocyte Colony Stimulating Factor
GnRH	Gonadotrophin Releasing Hormone
hCG	human Chorionic Gonadotrophin
HIF	Hypoxia Inducible Factor
IGF	Insulin Growth Factor

List of Abbreviations

IHC	Immunohistochemical
IQ	Intelligent Quotient
ITC	Isolated Tumor Cells
IUGR	Intra Uterine Growth Retardation
IVF	Invitro Fertilization
LCIS	Lobular Carcinoma Insitu
LH	Lutinizing Hormone
LHRH	Lutinizing Hormone Releasing Hormone
MTX	Methotrexate
PDGF	Platelete Drived Growth Factor
p.i	post injection
PR	Progesteron Receptor
RR	Relative Risk
RT-PCR	Reverse Transcriptase-Polymerase Chain Reaction
SEER	Serveillence, Epidemiology & End Results
SLNB	Sentinel Lymph Node Biopsy
TGF	Transforming Growth Factor
TSH	Thyroid Stimulating Hormone
UV	Ultraviolet

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Introduction

Approximately 213,000 new cases of breast cancer were diagnosed in the US during 2006. Of these, 25% and 10% occurred in women younger than 50 and 40 years, respectively ***(Howe et al. 2006).***

As women are delaying childbearing for personal reasons, including cultural, educational, and professional reasons ***(Ventura 1989),*** there has been an increasing number of patients in whom breast cancer occurs before the completion of their reproductive project.

Breast cancer is a potentially curable disease when diagnosed early and if appropriate local and systemic treatment is delivered. Even very young women with breast cancer, who have a notably worse prognosis than older patients ***(Aebi et al. 2006),*** can now live longer and healthier: More effective and tailored therapies have become available as adjuvant treatment for early breast cancer, including dose-dense chemotherapy and trastuzumab ***(Smith et al. 2007).***

Moreover, the role of endocrine responsiveness in very young patients has been clarified ***(Colleoni et al. 2006),*** and innovative trials exploring the combination of LHRH analogs and aromatase inhibitors versus LHRH analogs and tamoxifen are ongoing ***(Goldhirsch et al. 2006).***

As a result of earlier diagnosis and better care, in the US and in most European countries, breast cancer mortality has been decreasing in all age cohorts since the beginning of the 1980s ***(Levi et al. 2007).***

Estrogens are causally linked to the development of breast cancer: Age at menarche, age at first full-term pregnancy, parity, breast feeding, and oral contraceptive use are some of the recognized factors that influence breast cancer incidence in young women ***(Russo and Russo 2006).***

Moreover, endocrine manipulation has been used as an effective treatment for advanced and early breast cancer, as recently confirmed by the EBCTG meta-analysis ***(Clarke 2006).*** For these reasons, the possible promotional effect of gestational estrogens on micrometastases has raised concern about the safety of a subsequent pregnancy in breast cancer patients.

The incidence of pregnancy-associated cancer is relatively low, complicating 0.02–0.1% of all pregnancies***. (Weisz et al. 2007; Koren et al. 2005; Pentheroudakis et al. 2006)***; This would translate into about 5000 annual new cases of pregnancy-associated cancer in the United States alone ***(Koren et al. 2005)***; However, the current trend to delay pregnancy and the age-dependent increase in the incidence of several malignancies ***(Koren et al. 2005)*** are expected to raise the occurrence of pregnancy-associated cancer. The diagnosis of cancer during pregnancy poses challenges to the woman, her family and the medical team.

The relative rarity of pregnancy-associated cancer precludes conducting large prospective studies to examine diagnostic, management and outcome issues and the literature is largely composed of small retrospective studies and case reports.

During pregnancy the woman's body undergoes physiological changes that may make the diagnosis of several cancers more challenging. Pregnancy-related increase in hormone levels causes breasts enlargement which makes it more difficult to notice small lumps. Furthermore, women and their physicians may mistakenly relate findings consistent with breast cancer to normal pregnancy-induced changes, leading to an average 5–7 months delay in the diagnosis of pregnancy-associated breast cancer ***(Zemlickis et al. 1992; Schedin 2006; Ezzat et al. 1996; Bonnier et al. 1996; Guinee et al. 1994; Lethaby et al. 1996; Ibrahim et al. 2000)*** A pregnant woman is at 2.5-fold higher risk of being diagnosed with advanced breast cancer than non-pregnant patients. ***(Zemlickis et al. 1992)***.

Cancer diagnosis requires tissue sampling and cytological examination. Most routine modes for tissue sampling, including open biopsies under local anesthesia, can be safely performed during pregnancy without harming the mother or fetus***. (Koren et al. 2005; Siddiq et al. 2006; Lieberman et al. 1999; Weisz et al. 2004)***; Interpretation of cytological specimens obtained during pregnancy may be challenging.

Physiological changes associated with pregnancy can lead to false-positive results and therefore the cytopathologist must be informed about the pregnancy. For example, the hyperproliferative state of the breast may lead to a relatively high rate of false-positive diagnosis of breast cancer. ***(Eedarapalli et al. 2006);*** Therefore, although open biopsy of a suspicious breast lesion during pregnancy may be problematic due to

breast hypervascularity and edema, it should be preferred to fine needle aspiration.

In most types of cancer the histopathological features are similar in both pregnant and non-pregnant patients. Histopathological evaluation of pregnancy-associated breast cancer specimens exhibit poor histologic and prognostic features. About 80% of specimens are estrogen or progesterone receptor negative, and there is an increased expression of HER-2/neu, P53 and Ki-67 nuclear antigen which are all poor prognostic markers ***(Middleton et al. 2003; Reed et al. 2003)***; Young women, pregnant or not, usually demonstrate biologically aggressive disease, and the histopathological features in pregnancy-associated breast cancer are similar to age matched non-pregnant women ***(Middleton et al. 2003)***

Fetal radiation exposure from most radiographic examinations is much lower than the threshold dose for adverse effects and should not present fetal risk ***(Koren et al. 2005; Kal et al. 2005)***; Therefore, if a diagnostic radiographic examination is medically indicated, the risk to the mother by not undergoing the procedure is usually much greater than the potential fetal risk. However, in many cases other types of examination that is not associated with radiation, such as MRI and ultrasonography, may provide the desired diagnostic information. This is especially important when there is a need for radiological examinations associated with high fetal radiation exposure such as abdominal or pelvic CT.

The increased glandularity and water content of the breasts during pregnancy may diminish the sensitivity of mammography in evaluating suspicious breast lumps ***(Lethaby et al. 1996)***; and several small retrospective studies suggested that breast ultrasonography has higher sensitivity than mammography in detecting malignant breast masses. ***(Ahn et al. 2003; Yang et al. 2006)***; during pregnancy, metastatic workup should be limited to patients with high probability of metastasis and only when their establishment may alter therapy.

The treatment of pregnancy-associated cancer is complex since it may be associated with adverse fetal effects. As in non-pregnant patients, therapeutic approaches of pregnancy- associated cancer include radiotherapy, chemotherapy and surgery.

The lack of clear information regarding the effect of radiation exposure during gestation has given rise to unjustified panic among the public ***(Fenig et al. 2001)***; the risk of fetal exposure to X-ray has been the subject of many studies. Generally, the effect of radiation on the fetus

depends on the gestational stage ***(Kal et al. 2005);*** Radiation exposure during organogenesis (weeks 2–8 after conception) can cause congenital malformations with a threshold dose of 0.1–0.2 Gy. ***(International Commission of Radiological Protection 2003)***; During weeks 8–25 after conception, the CNS is sensitive to radiation and a dose of 0.1 Gy can result in a decrease in intelligence quotient (IQ) ***(Fenig et al. 2001)***; During the same period, radiation doses of about 1 Gy are associated with up to 40% risk for severe mental retardation ***(Otake et al. 1998)***; After 25 weeks of gestation the effect of all radiation doses are much less striking ***(Kal et al. 2005).***

Radiation exposure during the second and third trimesters is associated with a carcinogenic effect that may include the development of leukemia and solid tumors within the first decade of life. Prenatal irradiation with fetal dose of 0.01 Gy is associated with 40% increase in the incidence of childhood cancer, to about 3–4 cases per 1000 children ***(Kal et al. 2005).***

Radiation doses used in cancer therapy are usually within the range of 4000–7000 cGy which is more than 1000-fold the level in diagnostic radiology ***(Fenig et al. 2001);*** Fetal exposure depends on several factors including the target dose, size of radiation fields and the distance from the edges of the fields to the fetus. Generally, a distance of over 30 cm from the field edges will yield an exposure of the fetus to only 4–20 cGy and therefore many areas such as the head, neck and extremities can be treated with radiation without significant fetal exposure ***(Fenig et al. 2001)***; Fetal radiation exposure should be measured individually and a qualified medical physicist should be consulted in each case before any treatment decisions are taken. For fetal doses of less than 0.1 Gy there is usually no medical justification for pregnancy termination ***(International Commission of Radiological Protection 2000)***; In doses above 0.2 Gy, especially during the first 15 weeks of gestation, the risk of IQ reduction and malformations must be seriously considered and the physician must make sure that the parents make their decision after being adequately informed.

Due to their relatively low molecular weight, most cytotoxic agents can cross the placenta and reach the fetus. When treating pregnant patients with chemotherapy, it is important to consider the physiological changes during pregnancy such as the increased plasma volume and renal clearance of drugs, faster hepatic oxidation and the third space created by the amniotic fluid. These changes might decrease active drug concentrations compared with women who are not pregnant and have the