Breast Cancer & Pregnancy

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Definitions

- Breast cancer during pregnancy
  vs.

- Pregnancy-associated breast carcinoma
  - Breast carcinoma that occurs during pregnancy or the lactation period up to 1 year after the end of pregnancy
Facts

• Second most commonly diagnosed solid tumor during pregnancy

• Incidence: estimated to occur in 1 per 3000 pregnancies
  - Expected to increase as more women delay child-bearing

• There is a perceived conflict between the optimal therapy of the mother with breast carcinoma and the well-being of the fetus
Pregnancy & Breast Cancer Risk

- Pregnancy may transiently increase risk of breast cancer
  - Cohort of 22K women with breast cancer
  - Compared to nulliparous women (incidence ratio=1), crossover to protection occurs nearly 10 years after first pregnancy

P Schedin: Nature Reviews Cancer, 2006
Clinical Presentation

• Most commonly presents as a painless, palpable mass

• Majority of tumors are of ductal origin (75-90%), high grade, and hormone receptor negative
  - Tumors of pregnant women with breast carcinoma are similar to those of nonpregnant young women with breast carcinoma

• Usually diagnosed at more advanced stages of disease
  - More difficult to detect secondary to physiologic breast changes during pregnancy; delay in diagnosis
  - Little difference in survival rates when compared to age and stage matched controls
Breast Imaging during Pregnancy

- Ultrasound is the diagnostic procedure of choice

- Mammography can be used safely with proper shielding
  - 10 rad increases the risk of fetal malformations by 1%
  - With adequate abdominal shielding, a mammogram results in less than 0.05 rad exposure to the embryo/fetus

- Breast MRI during pregnancy is not recommended
  - Gadolinium crosses the placenta and induces malformations in animal models
  - Difficulty in positioning pregnant patient on her stomach
Recommendations on Radiation Exposure during Pregnancy

“Exposure to less than 5 rad has not been associated with an increase in fetal anomalies or pregnancy loss.”
(American College of Obstetrics and Gynecology)

“Prenatal doses from most properly done diagnostic procedures present no measurably increased risk of prenatal death, malformation, or impairment of mental development over the background incidence of these entities.”
(International Commission on Radiological Protection)

“No single diagnostic procedure results in a radiation dose that threatens the well-being of the developing embryo and fetus.”
(American College of Radiology)
Breast Cancer Staging during Pregnancy

Breast Carcinoma during Pregnancy

International Recommendations from an Expert Meeting

- S Loibl: Cancer, 2006

• **Recommended**
  - Chest x-ray with abdominal shielding
  - Ultrasound of the liver
  - Noncontrast MRI of the thoracic and lumbar spine to exclude bone metastases

• **Not recommended**
  - Computed tomography scans
  - Bone scans
Treatment of Breast Cancer during Pregnancy

- Should conform as closely as possible to standardized protocols for patients without concomitant pregnancy

- Data regarding treatment for breast carcinoma in pregnancy is primarily from case reports, case-control studies, and historical cohort studies

- Special considerations
  - Gestational age at presentation
  - Stage of disease
  - Patient preferences
Breast Cancer Treatment during Pregnancy

- **Local**
  - Surgery
  - Radiation

- **Systemic**
  - Chemotherapy
  - Hormone therapy
Anesthesia & Pregnancy

- Teratogenicity
- Fetal asphyxia
- Preterm labor & delivery
Anesthesia & Pregnancy

Pregnancy outcome following non-obstetric surgical intervention

Raanan Cohen-Kerem, M.D.\textsuperscript{a}, Craig Railton, M.D., Ph.D.\textsuperscript{a}, Dana Oren, M.Sc.\textsuperscript{a}, Michael Lishner, M.D.\textsuperscript{b}, Gideon Koren, M.D.\textsuperscript{a,*}

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\textsuperscript{b}Department of Medicine A, Meir Hospital, Kfar-Saba, Israel

R Cohen-Kerem: Am J Surgery, 2005

- Retrospective analysis of 54 studies including over 12,000 patients around the world
- No increase in maternal death, spontaneous abortion, or birth defects secondary to anesthesia
- “Surgery in the first trimester does not appear to increase major birth defects and should not be delayed when indicated”
Surgery & Pregnancy

• Modified radical mastectomy represents the most common means of surgical management

• There is no data regarding breast conservation
  - Cannot administer radiation therapy during pregnancy
  - Concerns about local control
  - Possibility of poor cosmetic outcome

• There is no data regarding sentinel lymph node biopsy
  - Isosulfan blue = possibility of anaphylaxis; category C in pregnancy
  - Methylene blue has been reported to cause intestinal atresia; category C in pregnancy
  - With technetium, the radiation dose to fetus calculated to be a maximum of 0.43 rad
Breast Cancer Treatment during Pregnancy

- Local
  - Surgery
  - Radiation

- Systemic
  - Chemotherapy
  - Hormonal therapy
Chemotherapy & Pregnancy

- Risk of congenital malformation from chemotherapy administered during the first trimester ranges from 10 to 20%.

- Risk of congenital malformation from chemotherapy declines to approximately 1.3% in the second and third trimesters.
Standard Chemotherapy

- Cyclophosphamide, methotrexate, 5-fluorouracil (CMF)
- CMF vs. cyclophosphamide, doxorubicin, & 5-fluorouracil (CAF)
- Doxorubicin & cyclophosphamide (AC), add taxane if node positive
- AC vs. taxotere & cyclophosphamide (TC)
- Trastuzumab
Chemotherapy & Pregnancy

- Methotrexate is abortofacient
- There is no data regarding taxanes
  - There are studies that show a strong placental expression of drug extruding transporters like P-glycoprotein and others that suggest that tubulin-binding agents (like paclitaxel) can be safely given during the second and third trimesters
  - Case reports indicate that taxanes can be safely administered during pregnancy
- There is no data regarding trastuzumab
  - Assigned category B pregnancy risk based on trials in monkeys; placental transfer shown to occur but no apparent fetal harm
  - Case reports show problems with amniotic fluid
Chemotherapy & Pregnancy

• Cyclophosphamide, methotrexate, 5-fluorouracil (CMF)
• CMF vs. cyclophosphamide, doxorubicin, & 5-fluorouracil (CAF)
• Doxorubicin & cyclophosphamide (AC), add taxane if node positive
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• Trastuzumab
Chemotherapy & Pregnancy

• M.D. Anderson has reported the largest prospective series of BCP patients treated with cytotoxic chemotherapy in the 2\textsuperscript{nd} and 3\textsuperscript{rd} trimesters
  - CAF chemotherapy
  - No significant complications for the fetus or the infant
Childbirth & Breast Cancer

• Timing of delivery: when the maturation of the fetus is sufficient and when optimal in relation to the breast cancer treatment

• Delivery should occur approximately 3 weeks after the last dose of chemotherapy to minimize the risk of maternal and fetal neutropenia and subsequent infection

• If chemotherapy is to be continued after delivery, vaginal delivery is preferred & breastfeeding is contraindicated

• Delivery should occur in a hospital with neonatal support
Cases: M.N.

- 32 yo pregnant white female who noticed a mass in her left breast
- Ultrasound examination revealed several areas suspicious for malignancy in her superior left breast
- Mammogram revealed suspicious calcifications through the superior left breast
- Ultrasound-directed core needle biopsy revealed invasive ductal adenocarcinoma, 20% estrogen receptor positive, progesterone receptor negative, HER-2/Neu strongly positive
- Seen at CBCC at nine weeks gestation
Cases: M.N.

- Underwent left modified radical mastectomy at 10 weeks gestation
- Pathology revealed two foci of poorly differentiated invasive ductal adenocarcinoma (largest focus 2.5 cm), extensive DCIS, 0/13 lymph nodes positive for metastatic disease
- Six doses of FAC chemotherapy planned
- First chemotherapy dose administered at 16 weeks gestation
- Birth planned at 35 weeks gestation
- Trastuzumab & hormonal therapy will be administered following delivery
Cases: A.B.

- 34 yo pregnant WF who noted a large mass in her right breast
- Ultrasound revealed a 4 cm mass with ill-defined borders
- Core biopsy performed at approximately 23 weeks gestation revealed a poorly differentiated invasive ductal carcinoma that was hormone receptor negative and Her-2/Neu negative
- Seen at CBCC at almost 25 weeks gestation when she expressed an interest in breast conservation
- Received 3 doses of AC chemotherapy, delivered at 34 weeks, subsequently received 3 more doses of dose-dense chemotherapy
Cases: A.B.

- Following chemotherapy, staging studies revealed no evidence of disease (CXR & bone scan)
- Mammogram revealed no suspicious calcifications
- Ultrasound revealed a small spiculated mass in the prior area of concern
- Patient underwent right partial mastectomy following preoperative wire localization + sentinel lymph node biopsy
- Pathology revealed a microscopic focus of poorly differentiated adenocarcinoma; sentinel lymph nodes were negative for tumor
Cases: Z.M.

- 42 yo pregnant WF with a history of DCIS treated only with excision who noticed a lump in her right breast
- Ultrasound examination revealed multiple suspicious masses in the lateral right breast
- Core biopsy at 29 weeks gestation revealed infiltrating ductal adenocarcinoma, 30% estrogen receptor positive, 90% progesterone receptor positive, HER-2/Neu negative
- Seen at CBCC at 30 weeks gestation
- Delivered at 34 weeks by C-section at which time she also opted for bilateral mastectomies, sentinel lymph node biopsy was performed (tracer injected in the operating room following delivery of the baby)
Cases: E.T.

- 42 yo WF who was found to have an area of architectural distortion in her right breast on mammogram.
- Stereotactic core needle biopsy revealed invasive ductal adenocarcinoma, 70% strongly estrogen receptor positive, 95% strongly progesterone receptor positive, HER-2/Neu negative.
- Breast MRI revealed a 1.6 cm spiculated mass in the area of the known carcinoma.
- Axillary ultrasound revealed no sonographically abnormal lymph nodes.
- Scheduled for right partial mastectomy following wire localization + sentinel lymph node biopsy but called prior to the procedure to announce that she was pregnant.
Cases: E.T.

- Returned to CBCC for consultation
- Decision was made to omit the sentinel lymph node biopsy but to proceed with right partial mastectomy following preoperative wire localization
NSABP B-04
Schema

Operable Breast Cancer

Clinically Node-Negative
- Radical Mast.
- Total Mast.
- Total Mast. + XRT

Clinically Node-Positive
- Radical Mast.
- Total Mast. + XRT
NSABP B-04
Overall Survival—Clinically Negative Nodes

- No significant difference in overall survival
- Leaving positive nodes did not significantly increase the rate of breast cancer-related mortality

Fisher B: NEJM, 2002
Cases: E.T.

- Returned to CBCC for consultation
- Decision was made to omit the sentinel lymph node biopsy but to proceed with right partial mastectomy following preoperative wire localization
- Pathology revealed a 1.2 cm invasive ductal carcinoma arising within a fibroadenoma
- Medical oncology team sent the tumor block for an Oncotype DX assay
Better Tools

• **Oncotype DX**
  - A tool used to determine the need for chemotherapy in hormone receptor positive, lymph node negative breast cancer
  - RNA is extracted from formalin-fixed, paraffin embedded tumor and then purified
  - Analyzes the expression of a panel of 21 genes from a tumor specimen using RT-PCR
  - The expression of 16 genes is measured and then normalized to a set of 5 reference genes
  - A Recurrence Score is calculated from the gene expression results
  - The Recurrence Score correlates with a specific likelihood of distant recurrence at 10 years: low risk, intermediate risk, high risk
Oncotype DX

PATIENT REPORT
Patient: Doe, Jane
Sex: Female
DOB: 01/02/1969
Medical Record/Patient #: 55667771
Date of Surgery: 12/25/2008
Specimen ID/Block ID: SURG-0001

RESULTS
Recurrence Score ~ 10

CLINICAL EXPERIENCE
Patients with a Recurrence Score of 10 in the clinical validation study had an Average Rate of Distant Recurrence at 10 years of 7% (95% CI: 5%-9%).

The following results are from a clinical validation study with prospectively-defined endpoints involving 600 patients. The patients enrolled in the study were female, stage I or II, node negative, ER-positive breast cancer. For patient samples outside of these criteria, it is unknown whether the findings summarized in the Clinical Experience section are applicable.
Cases: E.T.

- Returned to CBCC for consultation
- Decision was made to omit the sentinel lymph node biopsy but to proceed with right partial mastectomy following preoperative wire localization
- Pathology revealed a 1.2 cm invasive ductal carcinoma arising within a fibroadenoma
- Medical oncology team sent the tumor block for an Oncotype DX assay
- Decision was made to allow a term delivery after which a sentinel lymph node biopsy will be performed
- Subsequent adjuvant therapy will be determined following sentinel lymph node biopsy
• When compared to age and stage matched controls, prognosis of breast cancer during pregnancy is equivalent

• Treatment of breast cancer during pregnancy should conform as closely as possible to standardized protocols for patients without concomitant pregnancy

• An interdisciplinary team (including gynecologists, medical oncologists, radiation oncologists, surgical oncologists, geneticists, etc) is required to formulate and implement the treatment plan along with the patient
Questions