Treatment of Breast Cancer in Pregnancy

Alison L Jones

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Number of new cases and rates by age, female breast cancer, UK
Trends in childbearing behaviour

• Decline in completed family size. Decrease from 2.46 children for 1934 cohort to 1.99 for most recent cohort to complete childbearing.

• Increase in proportion of women remaining childless. Increase from 9 per cent of women born in 1945 to around 20 per cent for women soon to complete childbearing.

• Increased mean age at first birth

• Childbearing to women in their 20s has decreased and increased to women in their 30s.
Definition

• Pregnancy-associated breast cancer is defined as carcinoma that is diagnosed during pregnancy or within 1 year postpartum (i.e., during lactation).
Incidence

- 1/1000 – 1/1500 term pregnancies
- Incidence increasing: delayed childbearing

<table>
<thead>
<tr>
<th>Frequency by Cell Type</th>
<th>Frequency in Reproductive Age Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast Cancer</td>
<td>30%</td>
</tr>
<tr>
<td>Lymphoma</td>
<td>10%</td>
</tr>
<tr>
<td>Leukemia</td>
<td>23%</td>
</tr>
<tr>
<td>Melanoma</td>
<td>30%</td>
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<tr>
<td>Cervix</td>
<td>35%</td>
</tr>
<tr>
<td>Ovary</td>
<td>15%</td>
</tr>
<tr>
<td>Bone/soft tissue tumors</td>
<td>25%</td>
</tr>
<tr>
<td>Thyroid</td>
<td>50%</td>
</tr>
</tbody>
</table>
What’s Different About Pregnancy?

- Hormones
- Metabolic Changes
- Hemodynamics
- Immunology
- Increased vascularity
- Age
- Few cases – anecdotal experience
- Inherent bias – breast, ovarian cancer
BREAST CANCER DURING PREGNANCY

Maternal Outcome  Fetal Outcome

Family outcome
(Current and future children)
Pregnancy Associated Breast Cancer; Treatment Goals

• Best chance of survival for the mother
• Protect the foetus and newborn from harmful effects of treatment

Include the Obstetrician and paediatrician as part of the extended multidisciplinary team
BREAST CANCER IN PREGNANCY
MATERNAL ISSUES

• Effect of pregnancy on cancer
• Effect of pregnancy on treatment decisions
• Effect of treatment on future fertility
• Effect of cancer and treatment on fetus
• Life expectancy and care of baby
• Future pregnancies
PREGNANCY AND BREAST CANCER SURVIVORSHIP ISSUES

• Woman’s chance of 5 and 10 year survival
• Impact of pregnancy on risk of recurrence
  – ER+ vs ER-
  – Duration of endocrine treatment
• Risk to baby
• Support for woman and family
Management of cancer during pregnancy per trimester (n = 215).

Van Calsteren K et al. JCO 2010;28:683-689
## Outcome of Women with Breast Cancer During Pregnancy

<table>
<thead>
<tr>
<th>Author</th>
<th>Patient No</th>
<th>Survival</th>
<th>Pregnant Patients</th>
<th>Controls</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zemlickis 1992</td>
<td>102vs269</td>
<td>10yrOS</td>
<td>40</td>
<td>48</td>
<td>ns</td>
</tr>
<tr>
<td>Ibrahim 2000</td>
<td>72vs216</td>
<td>5yrOS</td>
<td>55</td>
<td>51</td>
<td>ns</td>
</tr>
<tr>
<td>Petrek 1991</td>
<td>63vs176</td>
<td>5yr OS</td>
<td>61</td>
<td>73</td>
<td>ns</td>
</tr>
<tr>
<td>Zhang 2003</td>
<td>88 vs176</td>
<td>5yr OS</td>
<td>40</td>
<td>57</td>
<td>0.05</td>
</tr>
<tr>
<td>Ishida 1992</td>
<td>192vs 191</td>
<td>10yr OS</td>
<td>55</td>
<td>79</td>
<td>0.001</td>
</tr>
<tr>
<td>Bonnier 1997</td>
<td>154vs 308</td>
<td>5yr RFS</td>
<td>69</td>
<td>81</td>
<td>0.01</td>
</tr>
</tbody>
</table>
Presentation

- Most commonly presents as a painless, palpable mass
- Mean age of women is 33 years
- 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 non-pregnant 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
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
Breast Carcinoma during Pregnancy

International Recommendations from an Expert Meeting

- **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
Obstetric Considerations

- Obstetrical Considerations
  - First trimester foetal US: (? Dates)
  - Foetal parts US 16 weeks
  - Chromosome analysis
    - Amniocentesis: 15 weeks
    - CVS: Transcervical (except cervix ca) or transabdominal at 10-12 weeks
  - Deliver when mature
    - Live/Stillbirth ratio at 34 weeks
    - Betamethasone (foetal lung)
Breast Cancer Treatment

• Local
  – Surgery
  – Radiation

• Systemic
  – Chemotherapy
  – Hormonal therapy
Surgical points

• Breast conservation or mastectomy?
  – equally effective but potential problem with delay in radiotherapy

• Sentinel node or ANC?
  – Blue dye is not recommended
  – Tc99m-sulfur collouid; fetal dose < 4mGY
Anesthesia & Pregnancy

- Teratogenicity
- Fetal asphyxia
- Preterm labor & delivery
Pregnancy outcome following non-obstetric surgical intervention

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¹Motherisk Program, Division of Clinical Pharmacology and Toxicology, Department of Pediatrics, University of Toronto, Hospital for Sick Children, 555 University Ave., Toronto, Ontario, Canada M5G 1X8
²Department 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”
Radiotherapy

• Should be avoided through pregnancy unless life saving or for functional preservation (e.g. spinal cord compression)

• If essential fetal shielding should be used
CHEMOTHERAPY DURING PREGNANCY; DRUG CHARACTERISTICS & FETAL TRANSFER

- Low molecular weight
- High lipid solubility
- Low plasma protein binding
- Non-ionisation

- Many cytotoxics fulfill these characteristics.
### Fetal Development

#### Period of dividing zygote, implantation, and bilaminar embryo (weeks)

<table>
<thead>
<tr>
<th>1</th>
<th>2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morula</td>
<td>Blastocyst</td>
</tr>
<tr>
<td>Not susceptible to teratogenesis</td>
<td></td>
</tr>
<tr>
<td>Death of embryo and spontaneous abortion common</td>
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</tbody>
</table>

#### Main Embryonic Period (weeks)

<table>
<thead>
<tr>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>16</th>
<th>32</th>
<th>38</th>
</tr>
</thead>
<tbody>
<tr>
<td>TA, ASD, and VSD</td>
<td>Heart</td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Amelia, meromelia</td>
<td>Upper limb</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Amelia, meromelia</td>
<td>Lower limb</td>
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<td></td>
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<tr>
<td>Cleft lip</td>
<td>Upper lip</td>
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<td></td>
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<tr>
<td>Low-set malformed ears and deafness</td>
<td>Ears</td>
<td></td>
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<td></td>
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<tr>
<td>Microphthalmia, cataracts, glaucoma</td>
<td>Eyes</td>
<td></td>
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<tr>
<td>Enamel hypoplasia and staining</td>
<td>Teeth</td>
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<td></td>
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<td></td>
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<tr>
<td>Cleft palate</td>
<td>Palate</td>
<td></td>
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<tr>
<td>Masculinisation of female genitalia</td>
<td>External genitalia</td>
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#### Fetal Period (weeks)

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<th>8</th>
<th>9</th>
<th>16</th>
<th>32</th>
<th>38</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neural-tube defects</td>
<td></td>
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<td></td>
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<tr>
<td>Mental retardation</td>
<td></td>
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<td></td>
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<tr>
<td>CNS</td>
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</tbody>
</table>
# Effects of Maternal Chemotherapy by Gestational Stage

<table>
<thead>
<tr>
<th>Stage</th>
<th>Effect</th>
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</thead>
<tbody>
<tr>
<td>1&lt;sup&gt;st&lt;/sup&gt; Trimester</td>
<td>Miscarriage 20-30% Malformations 10-25%</td>
</tr>
<tr>
<td>2&lt;sup&gt;nd&lt;/sup&gt; and 3&lt;sup&gt;rd&lt;/sup&gt; Trimester</td>
<td>IUGR, Low birth weight Prematurity</td>
</tr>
<tr>
<td>Perinatal Period</td>
<td>Trasfer to breast milk</td>
</tr>
</tbody>
</table>
## Risk of Miscarriage/ Malformation by Drug Type

<table>
<thead>
<tr>
<th>HIGH</th>
<th>LOW</th>
<th>UNKNOWN</th>
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</thead>
<tbody>
<tr>
<td>Aminopterin</td>
<td>5FU</td>
<td>Taxanes</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>Doxorubicin</td>
<td>Platinums</td>
</tr>
<tr>
<td>Methtotrexate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chlorambucil</td>
<td>Daunorubicin</td>
<td>Rituximab</td>
</tr>
<tr>
<td>Busulphan</td>
<td>Vinca Alkaloids</td>
<td>Trastuzumab</td>
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<tr>
<td>Mustard</td>
<td>Cyclophosphamide</td>
<td>Laptinib</td>
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<tr>
<td>Procarbazine</td>
<td>Interferon</td>
<td>Bevacizumab</td>
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<tr>
<td>Ara-C</td>
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<tr>
<td>ATRA</td>
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<tr>
<td>Tamoxifien</td>
<td></td>
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</tr>
<tr>
<td>Drug</td>
<td>Maternal Factors</td>
<td>Foetal Factors</td>
</tr>
<tr>
<td>-------------------</td>
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<td>---------------------------------------</td>
</tr>
<tr>
<td>5 Fluorouracil</td>
<td>Renal excretion</td>
<td>3rd space distribution</td>
</tr>
<tr>
<td></td>
<td>Volume of distribution</td>
<td>Non-linear kinetics</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>Renal excretion</td>
<td>Enterohepatic reabsorption</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hepatic elimination</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Crosses placenta</td>
</tr>
<tr>
<td></td>
<td>Volume distribution</td>
<td>3rd space distribution</td>
</tr>
</tbody>
</table>

**Maternal Factors**

- Renal excretion
- Volume of distribution

**Foetal Factors**

- 3rd space distribution
- Non-linear kinetics
- Enterohepatic reabsorption
- Hepatic elimination
- Crosses placenta
- 3rd space distribution
- toxicity
CYTOTOXIC DRUGS AND PREGNANCY

**Maternal Factors**

**Doxorubicin**
- Hepatic excretion
- Volume of distribution
- Protein bound

**Cyclophosphamide**
- Renal excretion
- Protein bound
- Excretion in milk

**Foetal Factors**

- High concentration in lung, liver, kidney
- Reduced placental transfer
- Crosses placenta

**Outcome**

- ? Long-term (heart)
- ? Maternal efficacy
Chemotherapy & Pregnancy

• FEC is regimen with most experience
• There are limited 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 are limited 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
Herceptin

- Monoclonal antibody that blocks the human epidermal growth factor receptor 2 protein
- Currently there are only two reports of pregnant patients treated with trastuzumab, with normal pregnancy outcome.
- It is generally considered safe for people who are pregnant.
Supportive Drugs

• Ondansetron and metoclopramide are safe
• GCSF crosses placenta but no reported teratogenic effects in rats or humans
• Bisphosphonates; not recommended as cause bone and renal malformations in animal models
• Antibiotics; follow standard obstetric guidelines
Endocrine treatment

• Tamoxifen is teratogenic in rats (wavy ribs) and should not be used during pregnancy
• Anecdotal reports of malformation of female genital organs in women receiving tamoxifen during pregnancy
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
Breast Feeding

- Cytotoxic drugs are detected in breast milk
- Breast feeding is not recommended during chemotherapy
- At least 2 weeks should elapse from last chemotherapy to breast feeding
BREAST CANCER DURING PREGNANCY
ISSUES FOR FETUS

• Congenital abnormality
• Prematurity
• Low Birth Weight
• End organ Damage
• Cognitive Function
• Fertility
• Risk of Malignancy
  (acquired and genetic)
Gestational age and birthweight for infants exposed to chemotherapy in utero

Lubchenko et al. 1966
Metastases to Fetus/Placenta

- Only 50 cases in literature
- Melanoma (50% of reported cases)
- Leukemia: 1/100 affected pregnancies
- Lymphoma
- Breast
CHEMOTHERAPY IN UTERO: LATE EFFECTS

- Little direct data (despite NCI database)
- Extrapolate from survivors of childhood cancer
  - Growth: normal on completion of therapy
  - Gonadal function = alkylating agents cause later fertility in boys
  - Carcinogenesis = mutagenic effects of chemotherapy = genetics of familial cancer syndrome anecdotal reports only

Need for follow up protocol
Long-Term Follow-Up of Children Exposed to Chemotherapy In Utero

- Aviles et al, 2001 FU 84 children for median 19 years
  - Normal physical, neurological, psychological development
  - Normal sexual development (12 became parents)
  - No increased risk of second malignancy
- Nulman et al, 2001 Fu 111 children followed for 2-19 years
  - Normal physical and neurological development
PSYCHOLOGICAL ISSUES

• Support through termination, duration and severity of grief reaction.
• Support through early delivery.
• Issues regarding suppression of lactation.
• Anxiety about the children.
• Anxiety about future fertility.
Summary

• 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.
Decision Tree for PABC

Cancer in pregnancy

- **Trimester 3**
  - Consider delaying treatment until achieving fetal maturity
    - Impossible
      - Chemotherapy may be administered
      - Radiation may be delivered after personal estimation of fetal dose
      - Plan delivery to non-cytopenic period
    - Possible
      - Delay treatment with close observation

- **Trimester 2**
  - Consider delaying treatment until achieving fetal maturity
    - Impossible
      - Radiation >0.1-0.2 Gy
    - Possible
      - Consider pregnancy termination

- **Trimester 1**
  - Radiation >0.1-0.2 Gy
  - Chemotherapy
    - No indication for pregnancy termination
    - Avoid treatment with anti-metabolites

Figure 1 Suggested decision tree for the treatment of cancer during pregnancy.