Breast Cancer, Pregnancy and Fertility
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Disclosures

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• Advisory Boards: Novartis and Pfizer (uncompensated)
NCCN, NIH PDQ

• UptoDate

Objectives

Upon completion of this lecture, participants will be able to:

• Discuss available information regarding pregnancies during and after breast cancer

• Review available fertility preservation options
Pregnancy and Cancer?

- Alcohol
- Raw or seared seafood
- Caffeine
- Red meat
- Hot dogs
- Deli meat
- Raw eggs
- Unpasteurized dairy

Epidemiology

Breast Cancer in Females by Single Year of Age at Diagnosis, SEER 17, 2000-2005
Is The Rate of Cancer Diagnosed During Pregnancy Increasing?

- Australian registry (1994 – 2007)
  - Increased from 112.3 to 191.5/100,000 deliveries
  - 16.0 to 37.4/100,000

Andersson T. et al Obstet & Gynecol 2009

BRCA1 and BRCA2 Mutations and Pregnancy-Associated Breast Cancer (PABC)

- Multiple cohort studies reporting:
  - Women with germline BRCA1 mutations more likely to have PABC than BRCA2 carriers
  - Women with BRCA2 mutations may have increased risk of breast cancer after pregnancy
  - Recent data also suggests BRCA1 mutation may be associated with low oocyte reserve
  - Women with a BRCA mutation and breast cancer history who are diagnosed during pregnancy or became pregnant after, there was no difference in survival

Johannsson O et al., Lancet 1998 352(9137):1359
Cullinane CA et al., Int J Cancer 2005 117(6):988
Oktay K et al., J Clin Oncol 2010 28(2):240
Valentini A et al., Breast Cancer Res Treat 2013 140(2):249
Diagnostic Imaging

- Palpable mass that does not resolve?
- Mammography
- Estimated fetal radiation exposure 0.007-0.02 cGy
- Breast Ultrasound: UT MD Anderson Cancer Center review breast and nodal basin ultrasound identified 100%
- MRI of the breast: no published data

Staging Investigations in the Pregnant Breast Cancer Patient

- Suspicious regional nodal disease: ultrasound and FNA (cytology)
- CXR: (<0.005 cGy)
- Abdominal ultrasound
- Bone scan: difficult
- Screening noncontrast MRI of the spine

Breast Cancer During Pregnancy: Pathologic Diagnosis

- FNA: cytology may be difficult to interpret due to proliferative changes of pregnancy
- Core biopsies: definitive histology, safe and only one case report of milk duct fistula
- Need ER/PR/HER-2/neu


Hahn KM et al., Cancer 2006 107(6):1219
Pathologic Features of Breast Cancer Diagnosed During Pregnancy

- Case series and case-control studies of pregnant women with breast cancer:
  - Majority of tumors ER (-) and PR (-)
  - HER-2/neu expression: 29% to 58% for HER-2/neu over-expression or amplification
  - Invasive ductal and poorly differentiated and often diagnosed at more advanced stages

Tobon H, Horowitz LF. Breast Dis 1993 6:127
Ishida T et al., Jpn J Cancer Res 1992 83(11):1143
Middleton LP et al., Cancer 2003 98(5):1055
Hahn KM et al., Cancer 2006 107(6):1219
Ring AE et al., J Clin Oncol 2005 23(18):4192
Elledge Rm et al., Cancer 1993 71(8):2499

Locoregional Options

Treatment of the Pregnant Breast Cancer Patient: Surgery

- Surgery during pregnancy
  - Increased rate of spontaneous abortions with general anesthesia
  - Increase in low and very low birth weight infants as well as intrauterine growth restriction (IUGR)
  - Unclear if this is due to underlying illness?
  - Mastectomy and pregnancy: No difference in fetal abnormalities

Duncan PG et al., Anesthesiology 1986 64(6):796
Breast Conserving Surgery in the Pregnant Woman with Breast Cancer

- Technically feasible - but radiation therapy required
  - Radiation exposure to the fetus increases as pregnancy
    proceeds secondary to greater proximity of the fetus to
    the radiation field (breast or chest wall)
  - Radiation needs to be timed with other therapies to be given
    after delivery

Annane K et al., Fetal Diagn Ther 2005 20(5):442

MD Anderson Surgery Experience

Of 67 patients:
- 30 had preoperative chemotherapy, 10 had breast
  conserving surgery (BCS) and 20 had mastectomy
- 37 with upfront surgery, 28 mastectomy and 9 BCS
- No difference in complications between mastectomy
  and lumpectomy
- No significant complications from core biopsies

Dominici LS and Litton JK et al., Breast Dis 2010 31(1):1

Chemotherapy and Endocrine Therapy
Systemic Therapy

- Retrospective case series - often non-uniform treatments
- Anthracyline based therapies have the most supporting evidence: AC, FAC, FEC when given in 2nd and 3rd trimesters
- Limited dose dense anthracycline safety and tolerance data
- Given at actual weight dosing

Chemotherapeutic Treatment of Pregnant Breast Cancer Patients (MD Anderson)

- After the 1st trimester: adjuvant or neoadjuvant FAC every 21-28 days:
  - 5-fluorouracil: 500 mg/m² IV on days 1 and 4
  - Doxorubicin: 50 mg/m² IV continuous infusion over 72 hours
  - Cyclophosphamide: 500 mg/m² IV on day 1 only
  - No therapy after 35 weeks
- Additional systemic therapies:
  - Trastuzumab postpartum
  - Tamoxifen after delivery

Non-anthracycline Based Therapies in Pregnant Breast Cancer Patients

- Methotrexate is contraindicated
- Taxanes – multiple case reports in breast and gynecologic cancers (now > 40 cases in the literature)
- 11 Case reports on trastuzumab: oligohydramnios and anhydramnios – FDA Category D
- 1 case report of lapatinib given in the first trimester
- Hormonal agents (tamoxifen) not recommended until after delivery

References:
De Santis M et al., Eur J Cancer Care (Engl) 2000 9(4):235
Gonzalez-Angulo AM et al., Clin Breast Cancer 2004 5(4):317
Kelly H, Clin Breast Cancer 2008 9(3):294
Prognosis

- Compared to 865 non-pregnant breast cancer patients, 311 women mostly from Germany and Belgium were analyzed, 2003-2011.
- Patients accrued both retrospectively and prospectively.

Results:

- Median age was 33 years for the pregnant and 41 years for the nonpregnant patients.
- Median follow-up was 61 months.
- The hazard ratio of pregnancy was 1.34 (95% CI, 0.93 to 1.91; p=0.14) for overall survival (OS).
- Cox regression estimated that the 5-year disease-free survival (DFS) rate for pregnant patients would have increased from 65% to 71% if these patients had not been pregnant.

Conclusion:

- The registry contained 447 women with breast cancer during pregnancy, mostly originating from Germany and Belgium.
- This information is important when patients are counseled and supports the option to delay treatment after delivery.

Multicenter European Experience

- Patients accrued both retrospectively and prospectively.
- 2003-2011
- 311 in analysis women mostly from Germany and Belgium.
- Compared to 865 non-pregnant breast cancer patients.
- No statistically significant difference in OS (HR 1.34, p=0.14)
Clinical Characteristics

Table 1. Characteristics by Case

<table>
<thead>
<tr>
<th>Variable</th>
<th>Pregnant Patients</th>
<th>Nonpregnant Patients</th>
<th>Missing Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>25</td>
<td>30</td>
<td>5</td>
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<tr>
<td>Prior cancer</td>
<td>10</td>
<td>12</td>
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<tr>
<td>Chemotherapy</td>
<td>60</td>
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<tr>
<td>Radiotherapy</td>
<td>10</td>
<td>10</td>
<td>0</td>
</tr>
<tr>
<td>Taxanes</td>
<td>70</td>
<td>68</td>
<td>2</td>
</tr>
<tr>
<td>HER2 positive</td>
<td>30</td>
<td>30</td>
<td>0</td>
</tr>
<tr>
<td>Grade 1</td>
<td>70</td>
<td>68</td>
<td>2</td>
</tr>
<tr>
<td>Grade 2</td>
<td>50</td>
<td>46</td>
<td>4</td>
</tr>
<tr>
<td>Grade 3</td>
<td>80</td>
<td>76</td>
<td>4</td>
</tr>
<tr>
<td>AJCC stage T1</td>
<td>30</td>
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<td>0</td>
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<tr>
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<td>50</td>
<td>46</td>
<td>4</td>
</tr>
<tr>
<td>AJCC stage T3</td>
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<td>18</td>
<td>2</td>
</tr>
<tr>
<td>AJCC stage N0</td>
<td>50</td>
<td>46</td>
<td>4</td>
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<tr>
<td>AJCC stage N1</td>
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<td>0</td>
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<tr>
<td>AJCC stage N2</td>
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<td>2</td>
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<tr>
<td>AJCC stage N3</td>
<td>10</td>
<td>10</td>
<td>0</td>
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Treatments

Table 2. Breast Cancer Treatment

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Pregnant Patients</th>
<th>Nonpregnant Patients</th>
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<tbody>
<tr>
<td>Neoadjuvant</td>
<td>2</td>
<td>2</td>
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<tr>
<td>Adjuvant</td>
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<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Mastectomy</td>
<td>1</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Breast conserving</td>
<td>1</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>None</td>
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<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>

Case Control: Chemotherapy during Pregnancy

Breast Cancer Study of Women Treated With Chemotherapy for Breast Cancer During Pregnancy as Compared With Nonpregnant Patients With Breast Cancer

Litton, et al. Case Control

- 75 Patients
- 1989-2009
- Matched 2:1 with non-pregnant controls
- ALL treated with standard chemotherapy in 2nd and 3rd trimesters

Survival Estimates

<table>
<thead>
<tr>
<th></th>
<th>Disease-Free Survival</th>
<th>Progression-Free Survival</th>
<th>Overall Survival</th>
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<tbody>
<tr>
<td>Time</td>
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<td>0-5</td>
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<td>5-10</td>
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<td>10-15</td>
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<td>15-20</td>
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<td>20-25</td>
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<td>25-30</td>
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<tr>
<td>95-100</td>
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</tbody>
</table>

Treatment of Breast Cancer During Pregnancy: Termination of Pregnancy

- Termination of pregnancy does not improve survival
- The decision to continue or terminate the pregnancy must be made by a woman who has been fully informed of the evidence, with regard to pregnancy termination
- Additional reasons to consider:
  - Known or suspected fetal teratogenesis
  - Health of the mother
Monitoring the Pregnancy During Chemotherapy

- Standard prenatal care
- Baseline ultrasound of the fetus
- Fetal growth evaluation before each chemotherapy cycle
- Amniocentesis if fetus at higher risk for karyotype abnormality
- If IUGR, oligohydramnios or severe anemia → doppler of the cord vessels

Outcomes in the Children

- 1st trimester 139 cases, 17% fetal malformation
- 2nd and 3rd trimester 150 cases, 1.3% fetal malformation
- Voluntary registry: 3.8% malformation
- UT MD Anderson Cancer Center: 3.8% (Down’s syndrome, ureteral reflux, clubfoot)
- European Cohort - from 7 countries, n=197 with chemo during pregnancy, multiple different regimens. IUGR 4%, no congenital abnormalities, stillbirth=1

Delivery and Neonatal Outcomes

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean gestational age at delivery (in weeks)</td>
<td>37 (range 29-41 weeks)</td>
</tr>
<tr>
<td>Mean birth weight (in kg)</td>
<td>2.9 (range 1.3-3.9 kg)</td>
</tr>
<tr>
<td>Type of delivery: Cesarean section</td>
<td>34.6% (27/78)</td>
</tr>
<tr>
<td>Any Neonatal complications at delivery</td>
<td>33.3% (3/63)</td>
</tr>
<tr>
<td>Breathing difficulties</td>
<td>17.5% (11/63)</td>
</tr>
<tr>
<td>Subarachnoid hemorrhage</td>
<td>1.6% (1/63)</td>
</tr>
<tr>
<td>Jaundice</td>
<td>4.8% (3/63)</td>
</tr>
<tr>
<td>Low heart rate</td>
<td>3.2% (2/63)</td>
</tr>
<tr>
<td>Hypoglycemia</td>
<td>3.2% (2/63)</td>
</tr>
<tr>
<td>Abnormal temperature</td>
<td>3.2% (2/63)</td>
</tr>
</tbody>
</table>

Loibl S et al., Cancer 2006 106(2):237
Dunn JS Jr et al., Obstet Gynecol 1999 94(5 Pt 2):846
Lamont RF et al., Obstet Gynecol 2003 101(3):516
Doll DC et al., Semin Oncol 1989 16(5):337
Cardonick E et al., Cancer J 2010 16(1):76
Litton JK et al., J Clin Oncol 2011 29(15s):1099
Loibl et al., Lancet Oncol 2012 13(9): 887-896
Pregnancy After a Diagnosis of Breast Cancer

Survivorship and Fertility Concerns

• Young Survivors
  – 657 young survivors were surveyed
  – 57% were concerned about infertility
  – 29% fertility concerns influenced their therapy
  – 72% discussed infertility concerns with their doctor
    but only 51% felt concerns were addressed adequately

Partridge AH et al., J Clin Oncol 2004 22(20):4174

Pregnancy and BRCA
BRCA and outcomes after pregnancy

- Valentini et al.
  - 1284 BRCA+ women
  - 128 diagnosed during pregnancy or became pregnant afterwards
  - Matched to 269 mutation carriers with breast cancer who did not have a subsequent pregnancy
  - NO difference in survival rates

- Kotsopoulos et al.
  - Matched case control of 1380 pairs of women with a BRCA mutation and a history of infertility, use of IVF or other fertility medications
  - 16% reported fertility problems
  - 4% used fertility medications
  - NO increase risk of the use of fertility medications identified


BRCA and age of onset of menopause

- Finch, et al. 2013 survey
  - 908 matched pairs of carriers and true negative non-carriers
  - Menopause: BRCA1 48.7, BRCA2 49.2, controls 50.3
  - Infertility and parity similar in both groups
  - Menopause before age 40: 4.7% (BRCA) vs. 1.4% (noncarriers)

- Collins, et al. 2013 survey
  - 1840 cases and controls
  - No difference in age of menopause
  - More BRCA carriers censored due to cancers and surgeries.


Pregnancy After Breast Cancer

<table>
<thead>
<tr>
<th>Study (year)</th>
<th>Pregnant</th>
<th>Not pregnant</th>
<th>Study design</th>
<th>Overall survival RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cooper (1970)</td>
<td>28</td>
<td>96</td>
<td>Matched case control</td>
<td>0.64 (0.31 – 1.33)</td>
</tr>
<tr>
<td>Hylden (1986)</td>
<td>48</td>
<td>130</td>
<td>Matched case control</td>
<td>0.80 (0.44 – 1.44)</td>
</tr>
<tr>
<td>Ariel (1989)</td>
<td>46</td>
<td>800</td>
<td>Population based</td>
<td>0.85 (0.55 – 1.32)</td>
</tr>
<tr>
<td>Sankila (1994)</td>
<td>91</td>
<td>471</td>
<td>Matched case control</td>
<td>0.85 (0.50 – 1.43)</td>
</tr>
<tr>
<td>Malamos (1996)</td>
<td>21</td>
<td>222</td>
<td>Hospital based</td>
<td>0.65 (0.39 – 1.07)</td>
</tr>
<tr>
<td>Lethaby (1996)</td>
<td>14</td>
<td>334</td>
<td>Population based</td>
<td>0.78 (0.53 – 1.15)</td>
</tr>
<tr>
<td>Velentgas (1999)</td>
<td>53</td>
<td>265</td>
<td>Matched case control</td>
<td>0.80 (0.39 – 1.69)</td>
</tr>
<tr>
<td>Whelan (2000)</td>
<td>74</td>
<td>23</td>
<td>Matched case control</td>
<td>0.84 (0.29 – 2.50)</td>
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<tr>
<td>Haffner (2011)</td>
<td>34</td>
<td>398</td>
<td>Matched case control</td>
<td>0.44 (0.22 – 0.88)</td>
</tr>
</tbody>
</table>

Adapted from: Azim HA Jr et al., Expert Rev Anticancer Ther 2011 11(2) 287
**Pregnancy After Breast Cancer**

<table>
<thead>
<tr>
<th>Study (year)</th>
<th>Pregnant (n)</th>
<th>Not pregnant (n)</th>
<th>Study design</th>
<th>Overall survival RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mueller (2003)</td>
<td>328</td>
<td>2002</td>
<td>Matched case control</td>
<td>0.56 (0.41 – 0.71)</td>
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<tr>
<td>Blakely (2004)</td>
<td>47</td>
<td>323</td>
<td>Hospital based</td>
<td>0.47 (0.27 – 0.82)</td>
</tr>
<tr>
<td>Lee (2005)</td>
<td>131</td>
<td>3418</td>
<td>Population based</td>
<td>0.59 (0.37 – 0.92)</td>
</tr>
<tr>
<td>Verkooijen (2010)</td>
<td>199</td>
<td>9327</td>
<td>Population based</td>
<td>0.59 (0.37 – 0.92)</td>
</tr>
<tr>
<td>Largiller (2009)</td>
<td>118</td>
<td>782</td>
<td>Hospital based</td>
<td>0.32 (0.19 – 0.51)</td>
</tr>
<tr>
<td>Kroman (2008)</td>
<td>197</td>
<td>344</td>
<td>Matched case control</td>
<td>1.2 (0.8 – 2.0)</td>
</tr>
<tr>
<td>Verkooijen (2010)</td>
<td>482</td>
<td>8528</td>
<td>Population based</td>
<td>Not provided</td>
</tr>
<tr>
<td>Iqbal (2017)</td>
<td>112</td>
<td>5832</td>
<td>Retrospective Cohort</td>
<td>0.22 (0.10-0.49)</td>
</tr>
</tbody>
</table>


**Pregnancy After a Diagnosis of Invasive Breast Cancer**

- Data from 3 SEER populations (Seattle, Detroit, and Los Angeles) from 1980-1993/94
- Women < 45 years at diagnosis were linked to vital records data


**Pregnancy After a Diagnosis of Breast Cancer: SEER**

- Live births 10 or more months after diagnosis
- Matched to up to 12 controls
  - Matched on age at diagnosis
  - Race/ethnicity
  - Diagnosis year
  - Disease stage
  - Previous non-breast primary tumor
Pregnancy After a Diagnosis of Breast Cancer: SEER

- 329 women with a live birth ≥ 10 months
- 2088 women with no live birth controls
- Patient risk of dying (RR 0.54; 95% CI: 0.41 – 0.71) compared to controls

Mueller BA et al., Cancer 2003 98(6):1131

Pregnancy After a Diagnosis of Breast Cancer: SEER

- Decreased risk
- Women with local disease at diagnosis (RR= 0.59; 95% CI: 0.40 – 0.89)
- Women with regional disease at diagnosis (RR 0.54; 95% CI: 0.37 – 0.78)
- No difference women < 35 years versus ≥ 35 years at diagnosis

Mueller BA et al., Cancer 2003 98(6):1131

Singapore and Swedish Registries

Verkooijen HM et al., Br J Surg 2010 97(8):1253

Gave birth

Did not give birth

<table>
<thead>
<tr>
<th>Time after diagnosis (years)</th>
<th>Gave birth</th>
<th>Did not give birth</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>492</td>
<td>462</td>
</tr>
<tr>
<td>1</td>
<td>463</td>
<td>512</td>
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<tr>
<td>2</td>
<td>345</td>
<td>346</td>
</tr>
<tr>
<td>3</td>
<td>239</td>
<td>251</td>
</tr>
</tbody>
</table>

Cumulative mortality ratio

Standardized mortality ratio
Meta-Analysis

- 14 studies included
- 1,244 pregnancies (cases)
- 18,145 no further pregnancies (controls)
- Death: RR 0.59 (95% CI: 0.50 – 0.70)
- More significant in women < 35 and with node negative disease

Overall Survival Analysis

Timing of Pregnancies
How Long to Wait?

  - <3 months RR 1.7 (95% CI: 1.2 – 2.6)
  - 4-6 months RR 1.0 (95% CI: 0.55 – 1.9)
  - 7-9 months RR 0.38 (95% CI: 0.12 – 1.2)
  - 10-12 months RR 1.0 (95% CI: 0.23 – 4.8)
  - 2-3 years RR 0.49 (95% CI: 0.27 – 0.86)
  - 3-4 years RR 0.30 (95% CI: 0.12 – 0.71)
  - 4-5 years RR 0.19 (95% CI: 0.05 – 0.81)

Wait Time Recommendations

- Azim meta analysis: after 2 years, overall mortality: RR 0.55 (95% CI: 0.36 – 0.84)
  - No evidence of heterogeneity
- Verkooijen et al.
  - risk of death decreases the further from diagnosis of breast cancer; within 1-2 years 3-fold higher relative mortality vs. 4 years

Pregnancy and Breast Cancer

Summary

- Women diagnosed during pregnancy can be considered for surgery at any time and chemotherapy after the first trimester
- Anthracycline regimens have the most safety data to date, however, other agents such as taxanes and vinorelbine have been described
- Radiation, hormonal agents and trastuzumab should be administered after delivery
- Further long term follow up in the children exposed in utero is warranted