The Patter of Tiny Feet: Fertility Preservation Options for Young Women with Early Stage Breast Cancer

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What is the Problem?

- More than 20,000 women per year < age 45 are diagnosed with breast cancer in the U.S.
- Up to 97% either have HR+ disease and/or will receive chemotherapy
  - At risk for infertility and premature ovarian failure (POF)
- Approximately half of these survivors (close to 10,000 women) could desire fertility
  - Affected by delayed child-bearing
  - Impact on treatment choices
- Retrospective series suggest no impact of subsequent pregnancy on breast cancer outcome
- This is an important issue for oncologists and patients

Psychosocial Impact of Treatment-Related Infertility

- Young women with breast cancer have increased psychosocial distress and anxiety compared to older women.
- Loss of reproductive potential after cancer treatment results in worse long-term QOL due to unresolved grief and depression, and reduced life satisfaction.
- Data in cancer survivors mirrors that of infertile women without cancer.

Impact of Chemotherapy on Different Stages of Follicular Growth

FSH-independent growth initiation (primordial → primary)

>3 Months

FSH-dependent phase of follicle growth: E2 production

Reasoning for Fertility Preservation in Young Women with Breast Cancer

30-year-old desiring one child

AC+T dose dense chemotherapy

Egg reserve reduced to 40-year-old

5+ year delay for tamoxifen treatment

Egg reserve reduced to 45-50 year old

Pregnancy probability nearly 0%
Variables Impacting the Risk of Chemotherapy Induced Ovarian Failure

- Age
- Ovarian reserve
  - Difficult to measure
  - Markers include levels of anti-mullerian hormone (AMH), inhibin B, antral follicle count (AFC)
- Type of cytotoxic agent(s)
- Chemotherapy dose and schedule
- Duration of treatment
- Use of endocrine therapy
<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Treatment</th>
<th>Amenorrhea</th>
<th>Correlations/notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fornier et al (Cancer, 2006) Retrospective</td>
<td>166</td>
<td>AC/T (96% paclitaxel, 71% dose dense)</td>
<td>15% ≤40 yrs (25/166)</td>
<td>Age (p&lt;.01) 5 pregnancies</td>
</tr>
<tr>
<td>Abusief et al (Cancer, 2010) Retrospective</td>
<td>431</td>
<td>AC AC/T q 3 weeks AC/T dose dense AC/T + trastuzumab T = paclitaxel</td>
<td>Overall 65%</td>
<td>Age (p&lt;.0001 for trend) Tamoxifen &gt; age 40 (p .02) Time to menses recovery</td>
</tr>
<tr>
<td>Swain et al (BCRT, 2009) NSABP B30 prospective subset</td>
<td>2343</td>
<td>AC x 4, docetaxel x 4 AT x 4 TAC x 4</td>
<td>79.6%</td>
<td>Tamoxifen (p-0.003)</td>
</tr>
<tr>
<td></td>
<td>708</td>
<td>AC x 4 , docetaxel x 4 T = docetaxel</td>
<td>Age % (N)</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>≤ 40 13.3% (18/135)</td>
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<td></td>
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<td>40-49 70% (172/246)</td>
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<td></td>
<td>≥ 50 97% (49/50)</td>
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<td></td>
<td></td>
<td>62% ≤ 6 mos</td>
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<td>31% ≤ 12 mos</td>
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<td>7% &gt; 12 mos</td>
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</table>
## Is Pregnancy Safe After Breast Cancer?

<table>
<thead>
<tr>
<th>Ref</th>
<th>Year</th>
<th># cases</th>
<th>Risk ratio of death</th>
<th>Interval b/w dx and preg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sankila et al</td>
<td>1994</td>
<td>91 case control</td>
<td>0.2 (0.1-0.5, P&lt;0.05)</td>
<td></td>
</tr>
<tr>
<td>Von Schoultz et al</td>
<td>1995</td>
<td>50/2119</td>
<td>0.48 (0.18-1.29, P=0.14)</td>
<td></td>
</tr>
<tr>
<td>Velentgas et al</td>
<td>1999</td>
<td>54 case control</td>
<td>0.8 (0.3-2.3, P&gt;0.05)</td>
<td></td>
</tr>
<tr>
<td>Mueller et al</td>
<td>2003</td>
<td>438 case control</td>
<td>0.54 (0.41-0.71, P&lt;0.05)</td>
<td>sig↓ mortality when birth &gt;10 mo after diagnosis</td>
</tr>
<tr>
<td>Blakely et al</td>
<td>2004</td>
<td>47/383</td>
<td>0.71 (0.25-1.95, P=0.49)</td>
<td></td>
</tr>
<tr>
<td>Ives et al</td>
<td>2007</td>
<td>123/2539</td>
<td>0.59(0.37-0.95, P=0.03)</td>
<td>Sig ↓ mort &gt;2yrs after dx</td>
</tr>
<tr>
<td>Kroman et al</td>
<td>2008</td>
<td>371/10,236</td>
<td>0.73 (0.45-0.99, P=0.04)</td>
<td></td>
</tr>
</tbody>
</table>
Options for Preservation of Fertility

• GnRH Agonists
• Ovarian stimulation
  – Cryopreservation of embryos
  – Cryopreservation of oocytes
    - Success slightly lower using oocytes previously frozen compared to those fertilized fresh (6-9%)
• Experimental techniques
  – Immature oocyte retrieval with *in vitro* maturation
  – Cryopreservation of ovarian tissue
• Early referral to reproductive specialists (before surgery) allows earlier/multiple cryopreservation cycles with increased oocyte yield

GnRH Agonists

- Chemotherapy in prepubertal girls causes less ovarian damage than in older women

- Ovarian suppression: hypotheses
  - Decrease function of pituitary ovarian axis
  - Decrease ovarian perfusion
  - Direct gonadal effect

- Treat 10-14 days before start of chemotherapy
  - Allow flare followed by downregulation

- Alkylating agents induce amenorrhea by affecting the resting oocyte/primordial follicle
  - Not cell cycle specific
  - Do not require cell proliferation for cytotoxic action
## Randomized Trials of GnRH Agonists to Preserve Fertility in Breast Cancer

<table>
<thead>
<tr>
<th>Study</th>
<th>ER status</th>
<th>N (age)</th>
<th>Design</th>
<th>Primary outcome</th>
<th>Resumption of menses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elgindy 2013</td>
<td>HR-</td>
<td>100 'early', 50 'late' (18-40yo)</td>
<td>Chemo +/- triptorelin (agonist for early starters)</td>
<td>Menses at 12mo.</td>
<td>NS: 60 v 48% 72 v 52%</td>
</tr>
<tr>
<td>Munster 2012</td>
<td>73% HR+</td>
<td>49 (&lt; 44yo)</td>
<td>Chemo +/- triptorelin</td>
<td>≥ 3 menses in 6 mo + FSH &lt;40 FU 2 yrs</td>
<td>NS: 90 v 88%</td>
</tr>
<tr>
<td>Gerber 2011</td>
<td>HR-</td>
<td>60 (&lt; 46yo)</td>
<td>Chemo +/- goserelin</td>
<td>2 consecutive menses at 6 mo</td>
<td>NS: 70 v 56% Age adj: 70 v 66%</td>
</tr>
<tr>
<td>Leonard 2010*</td>
<td>NR</td>
<td>227 140 evaluable (62%&lt;40yo)</td>
<td>Chemo +/- goserelin</td>
<td>Any menses in 12 mo</td>
<td>NS: 65% v 84%</td>
</tr>
<tr>
<td>Badawy 2009</td>
<td>HR-</td>
<td>80 (med age 30)</td>
<td>Chemo +/- goserelin FAC q 6-8 wks x 6 mo</td>
<td>Menses w/in 3-8 mo</td>
<td>Sig: 90 vs 33% p&lt;.001</td>
</tr>
</tbody>
</table>

Median time to menses recovery: 5-6.7 months

*only published in abstract form
POEMS – S0230

- Phase III cooperative group trial
- Premenopausal, < age 50
  - Stage I – IIIA, ER/PR negative
  - Stratified by age and chemo regimen
- (Neo)adjuvant chemo with cyclophosphamide
  - Randomized to goserelin or not starting at least one week prior to start and through end of chemotherapy
- Primary endpoint: Ovarian failure at 2 years
  - No menses x 6 months + postmenopausal FSH
  - Secondary outcomes included pregnancy outcomes
- Planned 416 pts, to detect 15% reduction
  - Enrolled 257 pts, now powered for 20% reduction

POEMS: Patients and Toxicity

• 257 randomized, age 25-49, median 38
  – 218 (85%) evaluable for pregnancy, DFS, OS
  – 135 (53%) evaluable for ovarian failure

• Toxicity (n=124)
  – Grade II-IV toxicity increased from 24 to 48%

POEMS: Results

- Ovarian failure at 2 years (n=135)
  - 22 vs 8%, absolute difference 10 patients
    - Multivariate p=.08, stratified p=.04

- Pregnancy (n=218)
  - Attempted: 16 vs 24% (p=.12)
  - Achieved: 11 vs 21%
    - p=.03, adj OR 2.45, abs diff 10 patients
  - Delivery/pregnancy: 9 vs 18% (p=.04, OR 2.45)

- DFS 4 yr estimate: 78 vs 89% (p=.04, adj HR 0.47)

PROMISE-GIM6: Long-Term Results

- Originally published in 2011
  - Median FU 3.8 years (Del Mastro JAMA 2011)
  - Current results: median FU 7.3 years

- Primary endpoint: Ovarian failure at 1 year
  - No menses and postmenopausal FSH and E2

- Enrolled 281 patients
  - Primary analysis 268 (95%)
  - Long term outcome: 246 (88%)
  - About 80% HR+, 66% < 40 yrs

- Randomized to chemotherapy +/- triptorelin
  - Chemotherapy: most anthra-based, anthra/taxane, few CMF

PROMISE - Results

• Highly significant reduction in risk of ovarian failure at one year
  – ~26 vs 9%, p<.001, OR 0.28

• At > 7 years
  – Non-significant increase in number of pregnancies in treatment arm

• Cumulative incidence of menstrual resumption
  – 72 vs 64%, p=.071, HR 1.28

• DFS/OS similar

• Caveats
  – 226 (80%) pts with HR+ disease
    - Patients whose ovarian function resumed within 1 year received monthly triptorelin for at least 2 years
  – 93% received adjuvant endocrine therapy
Ovarian Stimulation for Fertility Preservation Prior to Chemotherapy

- **Ovarian Stimulation**
  - Uses controlled ovarian hyperstimulation
  - Takes about 2 weeks
  - Use of AIs for ovarian stimulation avoids high mid-cycle estrogen levels
  - Possible to freeze embryos or oocytes
Standard Antagonist Protocol for Embryo or Egg Freezing

<table>
<thead>
<tr>
<th>Variable</th>
<th>Tam-IVF</th>
<th>TamFSH-IVF</th>
<th>Letrozole FSH-IVF</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>36.6 ± 1.6</td>
<td>38.3 ± 1.9</td>
<td>36.2 ± 0.8</td>
<td>NS</td>
</tr>
<tr>
<td>Baseline FSH (mIU/ml)</td>
<td>9.4 ± 1.5</td>
<td>9.4 ± 1.5</td>
<td>7.2 ± 0.8</td>
<td>NS</td>
</tr>
<tr>
<td>Peak $E_2^*$ (pg/mL)</td>
<td>419 ± 39&lt;sup&gt;a,b&lt;/sup&gt;</td>
<td>1182 ± 271&lt;sup&gt;a&lt;/sup&gt;</td>
<td>405 ± 45&lt;sup&gt;a,b&lt;/sup&gt;</td>
<td>a &lt; 0.01 b &gt; 0.05</td>
</tr>
<tr>
<td>Total Follicle</td>
<td>2 ± 0.3&lt;sup&gt;a&lt;/sup&gt;</td>
<td>6 ± 1&lt;sup&gt;a,b&lt;/sup&gt;</td>
<td>8.3 ± 0.6&lt;sup&gt;a,b&lt;/sup&gt;</td>
<td>a &lt; 0.001 b &gt; 0.05</td>
</tr>
<tr>
<td>Follicle ≥17mm</td>
<td>1.2 ± 0.1&lt;sup&gt;a&lt;/sup&gt;</td>
<td>2.6 ± 0.4&lt;sup&gt;a,b&lt;/sup&gt;</td>
<td>3.6 ± 0.3&lt;sup&gt;a,b&lt;/sup&gt;</td>
<td>a &lt; 0.05 b &gt; 0.05</td>
</tr>
<tr>
<td>Total Oocyte</td>
<td>1.7 ± 0.3&lt;sup&gt;a&lt;/sup&gt;</td>
<td>6.9 ± 1.1&lt;sup&gt;a,b&lt;/sup&gt;</td>
<td>11.0 ± 1.2&lt;sup&gt;a,b&lt;/sup&gt;</td>
<td>a &lt; 0.001 b &gt; 0.05</td>
</tr>
<tr>
<td>Mature Oocyte</td>
<td>1.5 ± 0.3&lt;sup&gt;a,c&lt;/sup&gt;</td>
<td>5.1 ± 1.1&lt;sup&gt;a,b,c&lt;/sup&gt;</td>
<td>8.0 ± 0.9&lt;sup&gt;a,b&lt;/sup&gt;</td>
<td>a &lt; 0.001 b,c &lt; 0.05</td>
</tr>
<tr>
<td>Total 2-PN Embryo</td>
<td>1.3 ± 0.2&lt;sup&gt;a&lt;/sup&gt;</td>
<td>3.8 ± 0.8&lt;sup&gt;a,b&lt;/sup&gt;</td>
<td>5.3 ± 0.6&lt;sup&gt;a,b&lt;/sup&gt;</td>
<td>a &lt; 0.001 b &gt; 0.05</td>
</tr>
</tbody>
</table>

COSTLES is Superior to Tamoxifen

Random Start Letrozole-FSH Protocol for Oocyte/Embryo Cryopreservation in Breast Cancer

Random start IVF outcomes are similar to conventional
Study Diagram

Women with breast cancer stage ≤ 3 who underwent ovarian stimulation and cryopreserved embryos for fertility preservation (N = 131)

Have not yet returned (n = 98)

Returned to undergo 40 FETs (n = 33)

Underwent FET to self (18 FETs) (n = 18)

Underwent FET to gestational carrier (22 FETs) (n = 15)

Underwent FET once (n = 8)

Underwent FET twice (n = 7)

9 deliveries

11 children born

6 deliveries

10 children born

3 deliveries

4 children born

Only a quarter of those who underwent ovarian stimulation with letrozole plus FSH returned for embryo transfer in this 14-year-long study, although the characteristics of those who returned versus those who did not were similar.


<table>
<thead>
<tr>
<th>Outcome</th>
<th>Self-Transfers: No. (%)*</th>
<th>Mean ± SD</th>
<th>Gestational Carriers: No. (%)†</th>
<th>Mean ± SD</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Embryos transferred</td>
<td>2.11 ± 0.58</td>
<td></td>
<td>1.95 ± 0.65</td>
<td></td>
<td>.434</td>
</tr>
<tr>
<td>Implantation rate‡</td>
<td>14 of 37 (37.8)</td>
<td></td>
<td>19 of 44 (43.1)</td>
<td></td>
<td>.626</td>
</tr>
<tr>
<td>Clinical pregnancy per FET</td>
<td>12 of 18 (66.6)</td>
<td></td>
<td>14 of 22 (63.6)</td>
<td></td>
<td>.842</td>
</tr>
<tr>
<td>Miscarriage per FET</td>
<td>3 of 18 (16.6)</td>
<td></td>
<td>5 of 22 (22.7)</td>
<td></td>
<td>.634</td>
</tr>
<tr>
<td>Live birth per FET</td>
<td>9 of 18 (50.0)</td>
<td></td>
<td>9 of 22 (40.9)</td>
<td></td>
<td>.565</td>
</tr>
<tr>
<td>Twinning rate</td>
<td>2 of 9 (22.2)</td>
<td></td>
<td>5 of 9 (55.5)</td>
<td></td>
<td>.335</td>
</tr>
</tbody>
</table>

Abbreviations: FET, frozen embryo transfer; SD, standard deviation.
*18 FETs in 18 women.
†22 FETs in 15 women.
‡Implantation rate is the total No. of pregnancy sacs per total No. of embryos transferred.
Safety of Letrozole-Gonadotropin Protocol in Women with Breast Cancer: Long Term Follow Up

- Prospective cohort study of relapse free survival
- Stimulation (study, n=120) vs. no-stimulation group (control, n=217)
- Mean follow-up: 4.9 years in study group and 6.2 years in controls (p<0.001)
- Sub-group analysis
  - ER (+) vs. ER (−) breast cancer
  - Pre- vs. post-resection
  - BRCA (+) vs. BRCA (−)

Safety of Letrozole-Gonadotropin Protocol in Women with Breast Cancer

As part of education and informed consent before cancer therapy, oncologists should address the possibility of infertility with patients treated during their reproductive years and be prepared to discuss possible fertility preservation options or refer appropriate and interested patients to reproductive specialists. Clinician judgment should be employed in the timing of raising this issue, but discussion at the earliest possible opportunity is encouraged. Sperm and embryo cryopreservation are considered standard practice and are widely available; other available fertility preservation methods should be considered investigational and be performed in centers with the necessary expertise.
ASCO Recommendations on Fertility Preservation

• Discuss fertility preservation with all patients of reproductive age if infertility is a potential risk of therapy.

• Refer patients who express an interest in fertility preservation (and patients who are ambivalent) to reproductive specialists.

• Address fertility preservation as early as possible, before treatment starts.

Conclusions

• The use of GnRH agonists during chemotherapy to protect ovarian function remains controversial
  – Given lack of apparent risk, would consider in patients with ER negative disease with discussion of unknown benefits
  – Not a substitute for established methods but might contribute
  – Unclear benefit in patients with HR+ disease who need subsequent hormone therapy and possibly OS

• Established methods include embryo or oocyte cryopreservation (~2 weeks)
  – High cost is a major barrier, some financial support is available (public foundations)
Conclusions (2)

• Fertility options should be discussed with all women of child-bearing age who are diagnosed with breast cancer **BEFORE** starting treatment
  – Universally recommended by multiple international guidelines
  – Early referral is critical to maximize yield
• Poise study: predictors of ovarian insufficiency in young breast cancer patients
  – 200 pts to be enrolled, ongoing
  – Goal is to create an index to predict risk of OI
• Positive trial: taking a break from adjuvant hormone therapy for pregnancy
In the End, It’s All About Balancing Risk vs Benefit

No increased risk of disease recurrence or risk from minimal delay in rx start.
ENDOCRINE THERAPIES IN BREAST AND PROSTATE CANCERS: Important Considerations for Patient Management in 2015