Fertility preservation (in breast cancer)

Fedro Peccatori, MD PhD
European Institute of Oncology,
European School of Oncology
Milan, Italy
Fertility concerns of cancer patients

Racial, Socioeconomic, and Demographic Disparities in Access to Fertility Preservation in Young Women Diagnosed With Cancer

Joseph M. Letourneau, MD; James F. Smith, MD, MS; Erin E. Ebbel, BA; Amaranta Craig, BA; Patricia P. Katz, PhD; Marcelle I. Cedars, MD; and Mitchell P. Rosen, MD, HCLD

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Total Sample, n=918</th>
<th>Leukemia, n=121</th>
<th>Hodgkin Disease, n=286&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Non-Hodgkin Lymphoma, n=169&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Breast Cancer, n=223</th>
<th>Gastrointestinal Cancer, n=108</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at diagnosis, y, mean (SD)</td>
<td>31.5 (6.7)</td>
<td>28.3 (7.2)</td>
<td>27.9 (6.2)</td>
<td>31.6 (6.0)</td>
<td>36.3 (4.0)</td>
<td>34.9 (4.6)</td>
</tr>
<tr>
<td>Age at survey, y, mean (SD)</td>
<td>40.9 (8.4)</td>
<td>37.0 (8.3)</td>
<td>36.5 (8.0)</td>
<td>40.5 (7.1)</td>
<td>47.1 (5.9)</td>
<td>44.6 (6.2)</td>
</tr>
<tr>
<td>Years since diagnosis, mean (SD)</td>
<td>9.6 (4.4)</td>
<td>8.7 (4.3)</td>
<td>8.6 (4.4)</td>
<td>8.9 (3.9)</td>
<td>10.8 (4.5)</td>
<td>9.7 (4.0)</td>
</tr>
<tr>
<td>Children before treatment, No. (%)</td>
<td>476 (52%)</td>
<td>46 (38%)</td>
<td>105 (37%)</td>
<td>88 (52%)</td>
<td>163 (73%)</td>
<td>76 (70%)</td>
</tr>
<tr>
<td>Desiring children after treatment, No. (%)</td>
<td>504 (54%)</td>
<td>71 (59%)</td>
<td>181 (63%)</td>
<td>82 (49%)</td>
<td>104 (47%)</td>
<td>61 (56%)</td>
</tr>
</tbody>
</table>
Fertility concerns of breast cancer patients

47% of young patients with breast cancer want a baby
Fertility concerns of breast cancer patients in Mexico

Fertility concerns among breast cancer patients in Mexico

Cynthia Villarreal-Garza a, b, c, Bertha Alejandra Martinez-Cannon b, c, Alejandra Platas c, Alejandro Mohar a, c, Ann H. Partridge d, Arnoldo Gil-Moran b, Alan Fonseca c, Yoatzin Vega c, Enrique Bargallo-Rocha a, c, Servando Cardona-Huerta b, Yadira Estefany Lopez-Aguirre a, c, Regina Barragan-Carrillo b, c, Andrea Castro-Sanchez c, e, *

Table 2
Fertility concerns.

<table>
<thead>
<tr>
<th>Degree of concern</th>
<th>N</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very concerned</td>
<td>22</td>
<td>16.4</td>
</tr>
<tr>
<td>Somewhat concerned</td>
<td>17</td>
<td>12.7</td>
</tr>
<tr>
<td>Little concerned</td>
<td>20</td>
<td>14.9</td>
</tr>
<tr>
<td>Not concerned at all</td>
<td>75</td>
<td>56.0</td>
</tr>
</tbody>
</table>

44% of patients with breast cancer concerned about fertility
Fertility concerns of breast cancer patients in Mexico

Fertility concerns among breast cancer patients in Mexico

Cynthia Villarreal-Garza a, b, c, Bertha Alejandra Martinez-Cannon b, c, Alejandra Platas c, Alejandro Mohar a, c, Ann H. Partridge d, Arnoldo Gil-Moran b, Alan Fonseca c, Yoatzin Vega c, Enrique Bargallo-Rocha a, c, Servando Cardona-Huerta b, Yadira Estefany Lopez-Aguirre a, c, Regina Barragan-Carrillo b, c, Andrea Castro-Sanchez c, e, *

Table 3
Effect of infertility risk on patient treatment decisions.

<table>
<thead>
<tr>
<th>Treatment decisions</th>
<th>N</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>It did not affect my treatment decisions</td>
<td>104</td>
<td>77.6</td>
</tr>
<tr>
<td>I chose to take tamoxifen for less than 5 years</td>
<td>11</td>
<td>8.2</td>
</tr>
<tr>
<td>I chose one chemotherapy regimen over another</td>
<td>9</td>
<td>6.7</td>
</tr>
<tr>
<td>Rejected endocrine therapy</td>
<td>2</td>
<td>1.5</td>
</tr>
<tr>
<td>Other changes</td>
<td>8</td>
<td>6.0</td>
</tr>
</tbody>
</table>

In 23% of patients, concerns affected treatment decisions
Fertility concerns of breast cancer patients

Web-Based Survey of Fertility Issues in Young Women With Breast Cancer

Ann H. Partridge, Shari Gelber, Jeffrey Peppercorn, Ebonie Sampson, Katherine Knudsen, Marc Laufer, Randi Rosenberg, Michele Przypyszny, Alison Rein, and Eric P. Winer

657 patients, median age 32.9 years

57% seriously concerned about sterility

29% did not comply to their treatment because of fertility issues
Pregnancy rate after cancer: not all alike

5-10% of young patients with breast cancer have a pregnancy

Stensheim et al; Int J Cancer 2011

Analysis adjusted for education level, previous pregnancy age
Pregnancy after breast cancer

- Age at diagnosis > 35 years (mostly)
- Treatment chemo +/- prolonged hormonal Rx
- Fear of pregnancy high
- Low awareness of fertility preservation possibilities
Fertility preservation, doctors’ perspective

• 32% of patients did not recall discussing fertility issues with their doctors

• 37% of doctors never read fertility preservation guidelines

• 49% of doctors were confused about safety of pregnancy after breast cancer

Safety: meta-analysis

Safety of pregnancy following breast cancer diagnosis: A meta-analysis of 14 studies

Hatem A. Azim Jr. a,b, Luigi Santoro c, Nicholas Pavlidis d, Shari Gelber e, Niels Kroman f, Hamdy Azim g, Fedro A. Peccatori h,*
Safety: meta-analysis

14 studies
- 7 case control studies
- 4 population based studies
- 3 hospital based studies

1244 cases e 18145 controls
Follow-up 5-30 years

Data pooling using random effect

Original data from 3 studies

Sensitivity analysis and subgroup analysis
Safety: meta-analysis

All studies, 41% risk reduction
Safety: multicenter study in ER+ breast cancer

Prognostic Impact of Pregnancy After Breast Cancer
According to Estrogen Receptor Status:
A Multicenter Retrospective Study


ABSTRACT

Purpose
We questioned the impact of pregnancy on disease-free survival (DFS) in women with history of breast cancer (BC) according to estrogen receptor (ER) status.

Patients and Methods
A multicenter, retrospective cohort study in which patients who became pregnant any time after BC were matched (1:3) to patients with BC with similar ER status, adjuvant therapy, age, and year of diagnosis. To adjust for guaranteed time bias, each nonpregnant patient had to have a disease-free interval at least equal to the time existing between BC diagnosis and date of conception of the matched pregnant one. The primary objective was DFS in ER-positive BC (DFS in the ER-negative cohort, whole population, and overall survival (OS)) were secondary objectives. Subgroup analyses included DFS according to pregnancy outcome and BC-pregnancy interval. With a two-sided α = 5% and β = 20%, 645 ER-positive patients were required to detect a hazard ratio (HR) = 0.85.

Results
A total of 333 pregnant patients and 874 matched nonpregnant patients were analyzed of whom 866 patients had an ER-positive disease. No differences in DFS was observed between pregnant and nonpregnant patients in the ER-positive HR = 0.89, 95% CI: 0.67 to 1.24, P = 0.55 or the ER-negative HR = 0.75, 95% CI: 0.51 to 1.08, P = 0.12 cohorts; however, the pregnant group had better OS HR = 0.72, 95% CI: 0.54 to 0.97, P = 0.03. With no interaction according to HR status (P = 1). Pregnancy outcome and BC-pregnancy interval did not seem to impact the risk of relapse.

Conclusion
Pregnancy after ER-positive BC does not seem to reduce the risk of BC recurrence.

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BRIEF COMMUNICATION

Long-term Safety of Pregnancy Following Breast Cancer
According to Estrogen Receptor Status


Affiliations of Authors: Department of Medicine, Institute Jean Bordier and Université Libre de Bruxelles (ULB), Brussels, Belgium (H.A., M.P., M.J.P., F.A.P., H.A.); Department of Medical Oncology, Aarhus University Hospital, Denmark (N.K., N.R., A.D.-A., B.P., A.P.); Istituto Europeo di Oncologia, Milan, Italy (M.J.P., F.A.P.); Department of Medical Oncology, University Hospital of Cachan, France (O.C.); Department of Medical Oncology and Palliative Care, University of Bologna, Italy (M.D.G., M.D.A., M.I., F.A.P.); Department of Oncology, Brussels, Belgium (S.G.); Istituto Europeo di Oncologia, Milan, Italy (M.J.P., F.A.P.); Department of Internal Medicine, Amarena University of Bari (M.A., M.P., M.J.P., F.A.P., H.A.);

Correspondence to: Hatem A. Azim Jr., M.D., Ph.D., Department of Internal Medicine, Amarena University of Bari (IBU), Bari, Italy (e-mail: hatemazimjr@ibu.it).

Abstract
Safety of pregnancy in women with history of estrogen receptor (ER)-positive breast cancer remains controversial. In this multicenter case-control study, 333 patients with pregnancy after breast cancer were matched (1:3) to 874 nonpregnant patients of similar characteristics, adjusting for guaranteed time bias. Survival estimates were calculated using the Kaplan-Meier analysis, groups were compared with the log-rank test. All reported P values were two-sided. At a median follow-up of 7.2 years after pregnancy, no difference in disease-free survival was observed between pregnant and nonpregnant patients with ER-positive (hazard ratio [HR] = 0.89, 95% confidence interval [CI] = 0.70 to 1.16, P = 0.36) or ER-negative (HR = 0.75, 95% CI: 0.54 to 1.02, P = 0.09). OS was significantly different observed (HR = 0.67, 95% CI: 0.46 to 0.98, P = 0.03). ER-positive patients in the pregnant cohort had better OS (HR = 0.57, 95% CI: 0.36 to 0.93, P = 0.03). Abortion, time to pregancy, breastfeeding, and type of adjuvant therepy had no impact on patients' outcomes. This study provides reassuring evidence on the long-term safety of pregnancy in breast cancer survivors, including those with ER-positive disease.

Many physicians and patients remain concerned about the safety of pregnancy in breast cancer survivors, especially in women previously diagnosed with estrogen receptor (ER)-positive disease who should be regarded as potentially detrimental by medical advice or treatment (1-3). Prior results of our study showed that a subsequent pregnancy had no significant impact on breast cancer outcomes irrespective of ER status; however, median follow-up was relatively short (4-7 years after pregnancy). (4) Considering that women with ER-positive disease are at increased risk of long-term recurrence (5), these results might not have provided the needed reassurance regarding the safety of pregnancy in these patients. Future, larger, updated survival analysis at median follow-up of 7.2 years after pregnancy.

Details of study design and statistical analysis were previously reported (4). Briefly, this is a multicenter case-control study in which women had a pregnancy after breast cancer (pregnant cohort) were matched (1:3) to nonpregnant patients (nonpregnant cohort) according to ER status, nodal status, adjuvant treatment, age, and years of diagnosis. To adjust for guaranteed time bias, each nonpregnant patient should have been disease-free for a minimum time not inferior to the time...
Safety: multicenter study in ER+

Retrospective, multicenter cohort study (7 Institutions)

333 cases with pregnancy after breast cancer
874 non pregnant controls matched for ER, stage, adjuvant treatment, age, year at diagnosis (+ healthy mother effect)

Primary endpoint: DFS ER+ pts.
(Two sided test $\alpha=5\%$, $\beta=20\%$, 226 events and 645 pts for HR 0.65)

Secondary endpoints: DFS in ER- pts., OS

Subgroup analysis: DFS according to timing of pregnancy
DFS according to breastfeeding
Safety: DFS in ER+ patients

HR 0.91 (95% CI 0.67-1.24)
Safety: OS in ER+ patients

HR 0.89 (95%CI 0.61-1.29)
Safety: long term follow-up (7.2 years)

DFS in ER+ patients

- Disease-free survival, %
  - Nonpregnant cohort
  - Pregnant cohort

<table>
<thead>
<tr>
<th>Time, y</th>
<th>Nonpregnant</th>
<th>Pregnant</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.0</td>
<td>492</td>
<td>194</td>
</tr>
<tr>
<td>2.5</td>
<td>346</td>
<td>138</td>
</tr>
<tr>
<td>5.0</td>
<td>233</td>
<td>88</td>
</tr>
<tr>
<td>7.5</td>
<td>134</td>
<td>50</td>
</tr>
<tr>
<td>10.0</td>
<td>32</td>
<td>17</td>
</tr>
<tr>
<td>12.5</td>
<td>5</td>
<td>4</td>
</tr>
</tbody>
</table>

No. at risk
Safety: long term follow-up (7.2 years)

OS in ER+ patients

Overall survival, %

Time, y

Nonpregnant cohort
Pregnant cohort

No. at risk
Nonpregnant 492 381 213 114 48
Pregnant 194 148 86 48 24

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What women want to know

What is the risk of chemotherapy-induced infertility? Is there anything we can do to reduced it?
Assessing the risk of infertility

CRITICAL FACTORS:

✓ Age at diagnosis (oocyte quantity and quality)
✓ Drugs administered (schedule and dosage)
✓ Age at pregnancy (treatment duration)

http://oncofertility.northwestern.edu/about-us
http://www.savemyfertility.org/pocket-guides
http://www.fertilehope.org/tool-bar/risk-calculator-women-type.cfm
Assessing the risk of infertility

36 y/o N+ Luminal B tumor
ECx4 -> wPTX x12 -> LHRHa+Exemestane x 5y

Intermediate Risk
Approximately 30-70% of women develop amenorrhea post-treatment.

- CMF x 6 cycles in women ages 30-39
  (cyclophosphamide, methotrexate, 5-fluorouracil)
- CEF x 6 cycles in women ages 30-39
  (cyclophosphamide, epirubicin, 5-FU)
- CAF x 6 cycles in women ages 30-39
  (cyclophosphamide, doxorubicin, 5-FU)
- AC x 4 cycles in women ages 40 and older
  (doxorubicin, cyclophosphamide)

http://www.fertilehope.org/tool-bar/risk-calculator-women-type.cfm
### Ovarian toxicity: drugs

**Panel 1: Estimated risk of gonadal dysfunction with cytotoxic drugs**

<table>
<thead>
<tr>
<th>High risk</th>
<th>Medium risk</th>
<th>Low risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cyclophosphamide</td>
<td>Cisplatin</td>
<td>Vincristine</td>
</tr>
<tr>
<td>Ifosfamide</td>
<td>Carboplatin</td>
<td>Methotrexate</td>
</tr>
<tr>
<td>Chlormethine</td>
<td>Doxorubicin</td>
<td>Dactinomycin</td>
</tr>
<tr>
<td>Busulfan</td>
<td></td>
<td>Bleomycin</td>
</tr>
<tr>
<td>Melphalan</td>
<td></td>
<td>Mercaptopurine</td>
</tr>
<tr>
<td>Procarbazine</td>
<td></td>
<td>Vinblastine</td>
</tr>
<tr>
<td>Chlorambucil</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Ovarian reserve

Menopause
Ovarian reserve at chemotherapy

CHEMOTHERAPY

Menopause
Ovarian reserve at chemotherapy

CHEMOTHERAPY

Menopause

Human Ovarian Reserve from Conception to the Menopause

W. Hamish B. Wallace*, Thomas W. Kelsey²

IEO Istituto Europeo di Oncologia
Ovarian reserve at chemotherapy

CHEMOTHERAPY

Menopause

Human Ovarian Reserve from Conception to the Menopause

W. Hamish B. Wallace¹, Thomas W. Kelsey²

IEO
Istituto Europeo di Oncologia
Ovarian reserve estimation: AMH
Ovarian reserve estimation: AMH
Treatment duration and ovarian ageing

Treatment duration (age at pregnancy)
ECx4 -> wPTX x12 -> LHRHa+Exemestane x 5y
Treatment duration and ovarian ageing

Treatment duration (age at pregnancy)
ECx4 -> wPTX x12 -> LHRHa+Exemestane x 5y
Is there anything we can do?

THINK PROACTIVELY!

- Inform the patient about the risk of infertility
- Refer her to the reproductive endocrinologist asap
- Consider egg/embryo freezing before chemotherapy
- Consider LHRHa during chemotherapy
- Offer participation in clinical trials
clinical practice guidelines

Cancer, pregnancy and fertility: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†

F. A. Peccatori1, H. A. Azim Jr2, R. Orecchia3, H. J. Hoekstra4, N. Pavlidis5, V. Kesic6 & G. Pentheroudakis5, on behalf of the ESMO Guidelines Working Group*

1 Fertility and Procreation Unit, Division of Gynaecologic Oncology, European Institute of Oncology, Milan, Italy; 2 Department of Medicine, BiEAST Data Centre, Institut Jules Bordet, Université Libre de Bruxelles, Brussels, Belgium; 3 Department of Radiotherapy, European Institute of Oncology, Milan, Italy; 4 Department of Surgical Oncology, University Medical Centre Groningen, Groningen, The Netherlands; 5 Department of Medical Oncology, University of Ioannina, Ioannina, Greece; 6 Department of Obstetrics and Gynaecology, Faculty of Medicine, University of Belgrade, Belgrade, Serbia.

These Clinical Practice Guidelines are endorsed by the Japanese Society of Medical Oncology (JSMO)

JOURNAL OF CLINICAL ONCOLOGY

Fertility Preservation in Patients With Cancer: ASCO Clinical Practice Guideline Update

Kutluk Oktay, Brittany E. Harvey, Ann H. Partridge, Gwendolyn P. Quinn, Joyce Reinedke, Hugh S. Taylor, W. Harms Wallace, Erica T. Wang, and Alison W. Loren

J Clin Oncol 36. © 2018 by American Society of Clinical Oncology
Egg/embryo freezing before chemo

ISSUES RELATED TO OVARIAN STIMULATION

✓ Safety (high estrogen levels)
✓ Efficacy (does it work)
✓ Timing (when to start ovarian stimulation)
Safety: Controlled ovarian stimulation (Letrozole)
Safety: Controlled ovarian stimulation

Safety of Fertility Preservation by Ovarian Stimulation With Letrozole and Gonadotropins in Patients With Breast Cancer: A Prospective Controlled Study

Amr A. Azim, Maria Costantini-Ferrando, and Kushuk Oktay

VOLUME 26 • NUMBER 16 • JUNE 1 2008
Safety: Controlled ovarian stimulation

SINGLE CENTER STUDY (US)

FP = 120
Control = 217

MULTICENTRIC REGISTRY-BASED COHORT STUDY (SWE)

FP = 145
Control = 351

Efficacy: Egg/embryo freezing before chemo

PROBABILITY OF REPRODUCTIVE SUCCESS ACCORDING TO AGE AND # FROZEN OOCYTES

- **30-34**
  - At Least 1 Child
  - At Least 2 Children
  - At Least 3 Children

- **41-42**
  - At Least 1 Child
  - At Least 2 Children
  - At Least 3 Children

Number of Mature (MII) Oocytes Vitrified/Warmed
Effective method for emergency fertility preservation: random-start controlled ovarian stimulation

Hakan Cakmak, M.D., Audra Katz, R.N., Marcell I. Cedars, M.D., and Mitchell P. Rowan, M.D.
Division of Reproductive Endocrinology and Infertility, Department of Obstetrics, Gynecology, and Reproductive Sciences, University of California, San Francisco, California

Objective: To determine whether random-start controlled ovarian stimulation (COS), in which a patient is stimulated on presentation regardless of her menstrual-cycle phase, has outcomes similar to conventional early follicular-phase-start COS for fertility preservation in cancer patients.

Design: Retrospective cohort study.

Setting: Academic medical center.

Participants: Women newly diagnosed with cancer and in preparation for gonadotoxic therapy.

Intervention: Random-start controlled ovarian stimulation.

Main Outcome Measures: Primary outcome: number of mature oocytes retrieved; secondary outcome: pattern of follicular development, oocyte yield, and fertilization rate.

Results: The number of total and mature oocytes retrieved, oocyte maturity rate, mature oocyte yield, and fertilization rates were similar in random- vs. conventional-start COS cycles. No superiority was noted when comparing COS started in the late follicular (n = 120) or early follicular (n = 20). Additionally, the addition of leuprolide, in the case of estrogen-sensitive cancers, did not adversely affect COS outcomes or oocyte maturity and competence in either random- or conventional-start protocols.

Conclusions: Random-start COS is an effective as conventional-start COS in fertility preservation. This protocol would minimize delays and allow more patients to undergo fertility preservation and still proceed with cancer treatment within 1–3 weeks.

Fertil Steril 2013;00():00–00. ©2013 by American Society for Reproductive Medicine.

Key Words: Random-start, fertility preservation, controlled ovarian stimulation

Discus: You can discuss this article with its authors and other ASRM members at http://fertstertforum.com/yourarticle.

Safety and feasibility of performing two consecutive ovarian stimulation cycles with the use of letrozole-gonadotropin protocol for fertility preservation in breast cancer patients

Vivian Tran, M.D., a,b, Giovanni Bedroschi, M.D., a,b, Free Mey, Ph.D., a,b, and Kurtfri Oktay, M.D. a,b

a,b, Institute for Fertility Preservation, New York, b Laboratory of Molecular Reproduction and Fertility Preservation, Obstetrics and Gynecology, New York Medical College, Valhalla, New York, a,b, Data Management and Analysis Unit, Department of Pathology, New York Medical College, Valhalla, New York

Objective: To investigate the safety and feasibility of performing two consecutive ovarian stimulation cycles with the use of letrozole for fertility preservation in breast cancer patients.

Design: Retrospective cohort study.

Setting: Academic fertility preservation center.

Participants: Seventy-eight women ≥45 years, diagnosed with stage ≥2 breast cancer, who desired fertility preservation.

Intervention: Two consecutive cycles versus a single ovarian stimulation cycle with a letrozole-follicle-stimulating hormone (FSH) protocol.

Main Outcome Measures: Embryo or oocyte cryopreservation outcomes, time interval from surgery to chemotherapy, and breast cancer recurrence rates.

Results: Sixty-one patients underwent single-cycle stimulation and 17 received two stimulation cycles. The mean total number of oocytes harvested (16.4 ± 13.3 vs. 9.9 ± 5.0) and embryos generated (4.4 ± 3.9 vs. 3.7 ± 3.1) were statistically significantly higher in patients who underwent two cycles versus one cycle. The time interval from surgery to chemotherapy was similar between the two cycles and single-cycle groups (9.5 ± 1.6 vs. 9.5 ± 1.4). After a mean follow-up interval of 16.5 ± 13.6 months, the recurrence rates were similar between the two cycles (8 of 17) and single-cycle (12 of 40) patients.

Conclusions: It appears to be safe and feasible to perform two consecutive ovarian stimulation cycles to increase the oocyte/embryo yield for fertility preservation. Fertil Steril 2013;00():00–00. ©2013 by American Society for Reproductive Medicine.

Key Words: Breast cancer, conservative cycles, fertility preservation, leuprolide, ovarian stimulation

Discus: You can discuss this article with its authors and other ASRM members at http://fertstertforum.com/yourarticle.

Breast cancer is the most prevalent malignancy among reproductive-aged women in the United States. With improvements in diagnostic and therapeutic strategies, breast cancer mortality rates have significantly declined over the past several years. Advances in breast...
Consider LHRHa during chemo

Ovarian suppression using luteinizing hormone-releasing hormone agonists during chemotherapy to preserve ovarian function and fertility of breast cancer patients: a meta-analysis of randomized studies

M. Lambertini¹, M. Ceppi², F. Poggio¹, F. A. Peccatori³, H. A. Azim Jr⁴, D. Ugolini⁵, P. Pronzato¹, S. Loibl⁶,⁷, H. C. F. Moore⁸, A. H. Partridge⁹, P. Bruzzi² & L. Del Mastro¹⁰*

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Received 7 July 2015; revised 12 August 2015; accepted 1 September 2015
Consider LHRHa during chemo

Author                          | Odds Ratio (95% CI) | Events, Treated | Events, Controls |
--------------------------------|---------------------|-----------------|-----------------|
Badawy (2009)                   | 0.06 (0.02, 0.20)   | 4/39            | 26/39           |
Sverrisdottir 1 (2009)           | 0.19 (0.04, 1.06)   | 14/22           | 18/20           |
Sverrisdottir 2 (2009)           | 2.03 (0.31, 13.27)  | 27/29           | 20/23           |
Del Mastro (2011)                | 0.27 (0.14, 0.54)   | 13/148          | 35/133          |
Gerber (2011)                    | 0.56 (0.19, 1.62)   | 9/30            | 13/30           |
Munster (2012)                   | 1.09 (0.22, 5.52)   | 4/26            | 3/21            |
Elgindy 1 (2013)                 | 0.76 (0.18, 3.25)   | 4/25            | 5/25            |
Elgindy 2 (2013)                 | 1.00 (0.25, 4.00)   | 5/25            | 5/25            |
Song (2013)                      | 0.50 (0.25, 1.03)   | 15/89           | 27/94           |
Karimi-Zarchi (2014)             | 0.05 (0.01, 0.29)   | 2/21            | 14/21           |
Moore (2015)                     | 0.30 (0.10, 0.87)   | 5/66            | 15/69           |
Li M (2008)                      | 0.31 (0.11, 0.89)   | 8/31            | 17/32           |
Sun (2011)                       | 0.38 (0.06, 2.30)   | 3/11            | 5/10            |
Li Jw (2014)                     | 0.44 (0.04, 4.35)   | 1/54            | 3/73            |
Fixed effect (I≤ = 47.1%, p = 0.026) | 0.34 (0.25, 0.46)   | 114/616         | 206/615         |
Random effect                    | 0.36 (0.23, 0.57)   |                 |                 |

Favors LHRHa / Favors Controls

Lambertini et 2015, Annals of Oncology
Pooled analysis of five randomized trials investigating temporary ovarian suppression with gonadotropin-releasing hormone analogs during chemotherapy as a strategy to preserve ovarian function and fertility in premenopausal early breast cancer patients


Abstract GS4-01
<table>
<thead>
<tr>
<th>Definition of premature ovarian insufficiency (POI)</th>
<th>PROMISE-GIM6&lt;sup&gt;1,2&lt;/sup&gt;</th>
<th>POEMS/SWOG S0230&lt;sup&gt;3&lt;/sup&gt;</th>
<th>Moffitt-led trial&lt;sup&gt;4&lt;/sup&gt;</th>
<th>GBG-37 ZORO&lt;sup&gt;5&lt;/sup&gt;</th>
<th>Anglo Celtic Group OPTION&lt;sup&gt;6&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>No resumption of menstrual activity and postmenopausal levels of FSH and E2</td>
<td>Amenorrhea for the prior 6 months and postmenopausal levels of FSH</td>
<td>No maintenance of menses and no resumption of menses</td>
<td>No reappearance of two consecutive menstrual periods within 21 to 35 days</td>
<td>Amenorrhea with elevated FSH</td>
<td></td>
</tr>
<tr>
<td>Timing of POI after chemotherapy</td>
<td>12 months</td>
<td>24 months</td>
<td>24 months</td>
<td>6 months</td>
<td>Between 12 and 24 months</td>
</tr>
<tr>
<td>Sample size</td>
<td>281</td>
<td>257</td>
<td>48</td>
<td>60</td>
<td>227</td>
</tr>
<tr>
<td>ER status for eligibility</td>
<td>ER-positive and ER-negative</td>
<td>ER-negative only</td>
<td>ER-positive and ER-negative</td>
<td>ER-negative only</td>
<td>ER-positive and ER-negative</td>
</tr>
<tr>
<td>Upper age limit for eligibility</td>
<td>≤ 45 years</td>
<td>≤ 49 years</td>
<td>≤ 44 years</td>
<td>≤ 45 years</td>
<td>None</td>
</tr>
<tr>
<td>Type of GnRHa</td>
<td>Triptorelin</td>
<td>Goserelin</td>
<td>Triptorelin</td>
<td>Goserelin</td>
<td>Goserelin</td>
</tr>
</tbody>
</table>

Premature-Ovarian Insufficiency Rate

**Meta-analysis approach**

<table>
<thead>
<tr>
<th>Study</th>
<th>GnRHa Events/pts</th>
<th>Control Events/pts</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PROMISE-GIM6</td>
<td>16/148</td>
<td>40/133</td>
<td>0.29 (0.15, 0.57)</td>
</tr>
<tr>
<td>POEMS/SWOG S0230</td>
<td>5/66</td>
<td>15/69</td>
<td>0.33 (0.10, 1.14)</td>
</tr>
<tr>
<td>UCSF-led trial</td>
<td>3/26</td>
<td>2/21</td>
<td>1.17 (0.14, 9.55)</td>
</tr>
<tr>
<td>GBG-37 ZORO</td>
<td>6/28</td>
<td>13/29</td>
<td>0.54 (0.14, 2.07)</td>
</tr>
<tr>
<td>OPTION</td>
<td>21/95</td>
<td>41/107</td>
<td>0.41 (0.20, 0.81)</td>
</tr>
<tr>
<td>Overall (I≤=0%,p=0.73)</td>
<td>51/363</td>
<td>111/359</td>
<td>0.37 (0.25, 0.57)</td>
</tr>
</tbody>
</table>

*Odds ratio (OR) adjusted for age, estrogen receptor status, type and duration of chemotherapy administered

Post-Treatment Pregnancy Rate

GnRHa Group: 37/359 (10.3%)  
vs  
Control Group: 20/367 (5.5%)  

IRR* 1.83 (95% CI 1.06-3.15)  
P = .030

Meta-analysis approach

<table>
<thead>
<tr>
<th>Study</th>
<th>GnRHa Events/pts</th>
<th>Control Events/pts</th>
<th>IRR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PROMISE-GIM6</td>
<td>8/148</td>
<td>3/133</td>
<td>2.52 (0.67, 9.50)</td>
</tr>
<tr>
<td>POEMS/SWOG S0230</td>
<td>22/105</td>
<td>12/113</td>
<td>1.77 (0.87, 3.57)</td>
</tr>
<tr>
<td>OPTION</td>
<td>7/106</td>
<td>5/121</td>
<td>1.54 (0.49, 4.85)</td>
</tr>
<tr>
<td>Overall (I≤=0%,p=0.85)</td>
<td>37/359</td>
<td>20/367</td>
<td>1.82 (1.05, 3.14)</td>
</tr>
</tbody>
</table>

IRR, Incidence rate ratio

Disease-Free Survival/Overall Survival

Median follow-up = 5.0 years (IQR, 3.0–6.3 years)

**HR* 1.01 (95% CI 0.72–1.42)**

*Hazard ratio adjusted for age, estrogen receptor status, type and duration of chemotherapy administered and tumor stage

**HR* 0.67 (95% CI 0.42–1.06)**

*Hazard ratio adjusted for age, estrogen receptor status, type and duration of chemotherapy administered and tumor stage

IQR, interquartile range

---

A single-arm, phase II trial evaluating the pregnancy outcomes and safety of interrupting endocrine therapy for young women with endocrine responsive breast cancer who desire pregnancy.

**P**regnancy **O**utcome and **S**afety of **I**nterrupting **T**herapy for women with endocrine responsive **IVE** breast cancer (**POSITIVE**).

Study chair: Olivia Pagani (IBCSG/IOSI)
**TRIAL SCHEMA**

- ER+ early breast cancer
- <43 years at enrolment
- Completing 18-30 months of ET
- (SERMs alone, LH-RH analogue + SERM or AIs)

**Pregnancy desire**

1. Treatment interruption
2. 3 months’ wash out
3. 2 years’ break to allow: conception, delivery ± breast feeding or pregnancy failure

Resume ET to 5-10 years according to individual risk, institutional policy and patient’s preference
**Correlative Research**

**Screening/eligibility:**
- Patients with ER+ early breast cancer
- ≤42 years at enrollment
- Completing 18-30 months of ET (SERMs alone, GnRH analogue + SERM or AIs) \(^1\)
- Pregnancy desire

\(^1\) \(\pm\) CT
\(^2\) No more than 1 month prior enroll.

**Stop ET \(^2\)**

**ENROLLMENT**

- 0
- 3
- 6
- 12
- 24 mos
- 10 yrs

- Plasma for ctDNA
- Serum for ovarian function (AMH, FSH,E2)
- Serum PRL/TSH
- Transvaginal US (Optional AFC)

**Follow-up**

- ET resumption to complete 5 (±10) yrs
- 3-6 months post ET restart: Plasma for ctDNA

---

**Translational research**

- 2nd trimester of pregnancy: Plasma for ctDNA
- Serum progesterone
- Plasma for ctDNA
- Transvaginal US (AFC optional)
- Selected centers: Endometrial biopsy

- Serum for ovarian function (AMH, FSH,E2)
- Serum PRL/TSH

---

**IBCSG**
Conclusions

Oncologists’ Role in Patient Fertility Care
A Call to Action

Teresa K. Woodruff, PhD
Northwestern University Feinberg School of Medicine, Chicago, Illinois.

Kristin Smith, BS
Northwestern University Feinberg School of Medicine, Chicago, Illinois.

William Gradishar, MD
Northwestern University Feinberg School of Medicine, Chicago, Illinois.

Oncofertility is a term coined just a few years ago to address the urgent, unmet needs of young cancer patients who were offered life-preserving but fertility-threatening treatments. The issue for many oncologists was not that they did not want to provide options to their patients; rather, the option list and the physician groups on the fertility side were limited. This issue has largely been addressed and the remaining barriers are few. Here are answers to the questions most frequently asked of oncologists by patients.

1. Do patients care about fertility in the face of a cancer diagnosis? Yes, many studies conducted over the past 5 years have shown that young women and men are concerned about their endocrine health and the fertility consequences of cancer treatment. Patients who are not told about later fertility concerns at the time of diagnosis have stress levels in the range of posttraumatic stress disorder during survivorship. Thus, oncologists are urged to provide a fertility consultation to mitigate the long-term health consequence associated with treatment.

2. What amount of time is necessary for women

4. Is fertility care affordable? There is a great deal of work toward affordability of fertility care options by oncofertility clinics. Some insurance companies will cover fertility options as long as they are coded appropriately, using the cancer diagnosis. Certain advocacy organizations provide discounted services at specific clinics, free stimulation medications, and/or grants for patients undergoing fertility preservation. In today’s social media-fueled world, many patients find ways to cover the fertility costs through crowd funding and from friends and family. The bottom line is that all young males and females should be advised of the fertility threat of their cancer care to enable the financial decisions to be made by the patient, not by the clinician before any irreversible damage to the gonads is done.

5. What fertility preservation options are available? The number of options for males and females, from birth upwards, continues to increase as experimental options of ovarian and testicular tissue freezing come to fruition in centers around the globe. A detailed list of options is available on Northwestern’s oncofertility web-
Take home messages

✓ Chemotherapy may impair ovarian function. Age, drug type and dosage are the critical factors

✓ Early oncofertility counseling and prompt referral to the reproductive endocrinologist are essential for effective fertility preservation

✓ Egg or embryo freezing before chemotherapy + LHRHa administration can be used to improve results

✓ Dedicated research protocols for young women with cancer are warranted
Thank you!

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4th ESO-ESMO Latin-American Masterclass in Clinical Oncology

18-22 April 2018
Mexico City, Mexico

Chairs:
A. Cervantes, ES - N. Pavlidis, GR
R.A. Stahel, CH

Scientific Co-ordinators:
M. Aapro, CH - F. Cardoso, PT

Under the auspices of

CMO
SMeO

LATIN-AMERICA PROGRAMME
Cancer in pregnancy

Fedro Peccatori, MD PhD
European Institute of Oncology
European School of Oncology
Milan, Italy
Points of Discussion

- Epidemiology of cancer during pregnancy
- Staging during pregnancy
- Radiotherapy during pregnancy
- Chemotherapy during pregnancy
- Children outcome
- Breast cancer
  - Special considerations on surgical management
Epidemiology

- 1/100 cancers in reproductive age are diagnosed during pregnancy
- 1/1000 pregnancies are complicated with cancer
## Staging workup

<table>
<thead>
<tr>
<th>Location</th>
<th>Safe</th>
<th>Not safe</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Breast</strong></td>
<td>Ultrasound, Mammogram</td>
<td>MRI with gadolinium</td>
</tr>
<tr>
<td><strong>Chest</strong></td>
<td>X-rays, Low dose CT scan (first trimester) DW-MRI*</td>
<td>X-rays, CT scan (beyond first trimester)</td>
</tr>
<tr>
<td><strong>Abdomen</strong></td>
<td>Ultrasound /DW-MRI*</td>
<td>CT scan</td>
</tr>
<tr>
<td><strong>Bone</strong></td>
<td>DW-MRI*</td>
<td>Bone scan</td>
</tr>
<tr>
<td><strong>Brain</strong></td>
<td>DW-MRI*</td>
<td></td>
</tr>
<tr>
<td><strong>Whole body</strong></td>
<td>DW-MRI*</td>
<td>PET scan</td>
</tr>
</tbody>
</table>

* Without gadolinium
Diffusion-weighted MRI

- Exploits random motion of free water molecules within tissues
- In highly cellular tissues (cancer) water molecules movement is restricted and this can be detected in T2 sequences
- No need of contrast media/gadolinium
Whole body MRI for systemic staging of breast cancer in pregnant women

Fedro A. Peccatori a,1, Giovanni Codacci-Pisanelli b,1, Maria Del Grande a, Giovanna Scarfone c, Fabio Zugni d, Giuseppe Petralia e

a Fertility and Procreation Unit, Department of Gynaecological Oncology, European Institute of Oncology (IEO), Milan, Italy
b Department of Medical and Surgical Sciences and Biotechnology, University of Rome “La Sapienza”, Italy
c Fondazione IRCCS Ca’ Granda Ospedale Maggiore Policlinico, Milan, Italy
d Post-graduate School in Radiodiagnostics, University of Milan, Italy
e Department of Radiology, European Institute of Oncology (IEO), Milan, Italy

ARTICLE INFO

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Breast cancer in pregnancy
WB-MRI in pregnancy

ABSTRACT

When breast cancer is diagnosed during pregnancy, treatment should be as close, as possible to what is used in non-pregnant patients. This requires accurate local and systemic staging: ultrasound (US) is used for local staging and allows adequate evaluation of the liver and pelvis, but chest and bones cannot be explored and imaging techniques involving exposure to ionizing radiation would be needed. However, since imaging techniques involving ionizing radiation and the use of radionuclides should be limited, whole body magnetic resonance imaging (WB-MRI) without administration of contrast agent represents a very interesting alternative, but limited data is available. In this paper we describe the obstetrical and oncological outcome of 14 patients in whom breast cancer was diagnosed during the second or third trimester of pregnancy and that were staged using WB-MRI. Median age of the patient at diagnosis was 35 years (range 20–36), median gestational age at MRI was 30 weeks (range 13–32) and median age at delivery was 38 weeks (range 32–38). At birth, one new-born presented respiratory distress syndrome and one jaundice. We conclude that diffusion-weighted MRI is feasible accurate and safe for the mother and for the foetus. It may represent the staging technique of choice in pregnant women diagnosed with breast cancer after the first trimester of pregnancy.

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Diffusion-weighted Magnetic Resonance Imaging for breast cancer staging in pregnant women

Giovanni Codacci-Pisanelli, Fedro A. Peccatori, Maria Del Grande, Giovanna Scarfone, Fabio Zugni, Giuseppe Petralia
Radiotherapy during pregnancy

- Increased risk of fetal malformation, mental retardation with radiation exposure > 100 – 200 mGy

- This dose is not reached if RT to sites away from uterus (e.g. brain, head/neck) with adequate shielding

- Yet, uncertainty regarding risk of cancer / sterility exists even with low doses

Usually contraindicated
Radiotherapy during pregnancy

- A 6MeV electron beam (36 Gy/18ttt/25d)
- Four dosimeters were placed on the abdomen (estimated fetal dose 0.004 Gy).
- **Delivery**: CS at W35
- **Fetal weight**: 2,650 g
- **Apgar score** at 10min: 10/10
- **FU 11 years**: mother alive NED, child with normal development, good grades at school
# Chemotherapy during pregnancy

The table below illustrates the main embryonic period (weeks) with corresponding neural-tube defects, mental retardation, and central nervous system (CNS) defects.

<table>
<thead>
<tr>
<th>Period of dividing zygote, implantation, and bilaminar embryo (weeks)</th>
<th>Main Embryonic Period (weeks)</th>
<th>Fetal Period (weeks)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Not susceptible to teratogenesis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death of embryo and spontaneous abortion common</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Embryonic disc</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Morula</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blastocyst</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amnion</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neural-tube defects</td>
<td>Mental retardation</td>
<td>CNS</td>
</tr>
<tr>
<td>TA, ASD, and VSD</td>
<td>Heart</td>
<td></td>
</tr>
<tr>
<td>Amelia, meromelia</td>
<td>Upper limb</td>
<td></td>
</tr>
<tr>
<td>Amelia, meromelia</td>
<td>Lower limb</td>
<td></td>
</tr>
<tr>
<td>Cleft lip</td>
<td>Upper lip</td>
<td></td>
</tr>
<tr>
<td>Low-set malformed ears and deafness</td>
<td>Ears</td>
<td></td>
</tr>
<tr>
<td>Microphtalmia, cataracts, glaucoma</td>
<td>Eyes</td>
<td></td>
</tr>
<tr>
<td>Enamel hypoplasia and staining</td>
<td>Teeth</td>
<td></td>
</tr>
<tr>
<td>Cleft palate</td>
<td>Palate</td>
<td></td>
</tr>
<tr>
<td>Feminisation of female genitalia</td>
<td>External genitalia</td>
<td></td>
</tr>
<tr>
<td>Major congenital anomalies</td>
<td>Functional defects and minor anomalies</td>
<td></td>
</tr>
</tbody>
</table>
Chemotherapy during pregnancy

<table>
<thead>
<tr>
<th>Period of dividing zygote, implantation, and bilaminar embryo (weeks)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
</tr>
<tr>
<td>Morula</td>
</tr>
<tr>
<td>Embryonic disc</td>
</tr>
<tr>
<td>Not susceptible to teratogenesis</td>
</tr>
</tbody>
</table>

**First trimester**

- 3-4 weeks: Early organogenesis
- 5-8 weeks: Organogenesis continues
- 9-16 weeks: Organ function begins

<table>
<thead>
<tr>
<th>Fetal Period (weeks)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-8</td>
</tr>
</tbody>
</table>

- Mental retardation
- CNS
- Heart
- Ear
- Liver
- Lip
- Ears
- Eyes
- Teeth
- Cleft palate
- Palate
- Masculinisation of female genitalia
- External genitalia

- Functional defects and minor anomalies

Malformation rate 20%

Cardonick E et al; Lancet Oncol 2004
The role of placenta
## Maternal/fetal transfer of chemotherapy (apes)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Number</th>
<th>Drug detected in fetus (n)</th>
<th>% drug detected in fetus</th>
</tr>
</thead>
<tbody>
<tr>
<td>Doxorubicin</td>
<td>15</td>
<td>6</td>
<td>7.5 ± 3.2</td>
</tr>
<tr>
<td>Epirubicin</td>
<td>11</td>
<td>8</td>
<td>4.0 ± 1.6</td>
</tr>
<tr>
<td>Paclitaxel</td>
<td>11</td>
<td>7</td>
<td>1.4 ± 0.8</td>
</tr>
<tr>
<td>Docetaxel</td>
<td>9</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>4</td>
<td>3</td>
<td>25.1 ± 6.3</td>
</tr>
<tr>
<td>Carboplatin</td>
<td>7</td>
<td>7</td>
<td>57.5 ± 14.2</td>
</tr>
</tbody>
</table>

**Graphs:**

A) Tissue concentration (ng/g) for Doxorubicin:

- Liver
- Kidney
- Lung
- Heart
- Placenta

B) Tissue concentration (ng/g) for Epirubicin:

- Liver
- Kidney
- Lung
- Heart
- Placenta

C) Graphs showing maternal and fetal tissue concentrations for Doxorubicin and Epirubicin.

**References:**

van Calsteren et al; Gynecol Oncol 2011
## Anthracyclines during pregnancy (women)

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Study type</strong></td>
<td>Retrospective</td>
<td>Prospective</td>
<td>Prospective</td>
<td>Prospective</td>
</tr>
<tr>
<td></td>
<td>Multicentric</td>
<td>Monocentric</td>
<td>Monocentric</td>
<td>Registry</td>
</tr>
<tr>
<td><strong>N.</strong></td>
<td>28</td>
<td>57</td>
<td>20</td>
<td>197</td>
</tr>
<tr>
<td><strong>Regimen</strong></td>
<td>A(E)C=16 CMF=12</td>
<td>FAC (100%)</td>
<td>Weekly E (100%)</td>
<td>A-based=178 A(E)C (n=55) Taxane=14 CMF=15</td>
</tr>
<tr>
<td><strong>chemo</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>delivery</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Congenital malformations</strong></td>
<td>0</td>
<td>3/57 (5%)</td>
<td>1/20 (5%)</td>
<td>8/179 (4.5%)</td>
</tr>
</tbody>
</table>

## Taxanes during pregnancy (women)

<table>
<thead>
<tr>
<th>Number</th>
<th>55</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast cancer</td>
<td>39</td>
</tr>
<tr>
<td>Other</td>
<td>16</td>
</tr>
</tbody>
</table>

| - Paclitaxel | 33 |
| - Docetaxel | 19 |
| - Both | 3 |

### Neonatal outcome

| - Mean Gestational age at delivery | W 36 |
| - Foetal weight | 2400 g |
| - Early preterm delivery | 1 (2%) |
| - Foetal complications | Anaemia (n=1), neutropenia (n=1) |
| - Foetal malformations | Pyloric stenosis (n=1) |

# Cisplatin and carboplatin during pregnancy

<table>
<thead>
<tr>
<th>Number</th>
<th>48</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Cisplatin</td>
<td>47</td>
</tr>
<tr>
<td>- Carboplatin</td>
<td>1</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Single agent (61.7%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Combination with bleomycin, or taxanes (38.3%)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Neonatal outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Mean Gestational age at delivery</td>
</tr>
<tr>
<td>- Foetal weight</td>
</tr>
<tr>
<td>- Foetal complications</td>
</tr>
<tr>
<td>- Foetal malformations</td>
</tr>
</tbody>
</table>

Zagouri F et al; Obstet Gynecol 2013
**Pregnancy complications after gestational chemotherapy**

An increased risk of pregnancy complications “on average” in patients treated with chemo during pregnancy even if started after the 1st trimester.

<table>
<thead>
<tr>
<th></th>
<th>Obstetric complications</th>
<th>Fetal weight &lt;10th percentile</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Chemo</td>
<td>No chemo</td>
</tr>
<tr>
<td>Cardonick, 2010</td>
<td>22/104 (22%)</td>
<td>NR</td>
</tr>
<tr>
<td>Loibl, 2012</td>
<td>31/179 (17%)</td>
<td>15/149 (9%)</td>
</tr>
</tbody>
</table>
No impact on short-term fetal mortality

Anthracycline (N=328), Taxanes (N=84), Platinum (N=74)
Is it all about placental toxicity?

- Does chemotherapy during pregnancy impair placental vascularization, thus promoting Small for Gestational Age (SGA) or intrauterine growth restricted (IUGR) babies?
Children outcomes

Long-term cognitive and cardiac outcomes after prenatal exposure to chemotherapy in children aged 18 months or older: an observational study

Frédéric Amant, Kristel Van Calsteren, Michael J Halaska, Mina Mhallem Gziri, Wei Hui, Lieven Lagae, Michèl A Willemsen, Livia Kapusta, Ben Van Calster, Heidi Wouters, Liesbeth Heyns, Sileny N Han, Viktor Tomek, Luc Mertens, Petronella B Ottevanger
Long term effects of gestational chemotherapy on children (n=70)

✓ Child’s behavior, general health, hearing and growth was reported as in a general population

✓ Most of the children have an age-adequate neurological development (intelligence, attention, memory) and cardiac function

✓ Prematurity was frequently encountered, and was associated with impairment in cognitive development
IQ score increases with 2.5 (95% CI: 1.2-3.9) for each week increase in pregnancy duration (p= 0.0003).

Long-term cognitive and cardiac outcomes after prenatal exposure to chemotherapy in children aged 18 months or older: an observational study

Frédéric Amant, Kristel Van Calsteren, Michael J Hofaska, Mina Mhallem Gaziri, Wei Hui, Lieven Logae, Michiel A Willemsen, Livia Kapusta, Ben Van Calster, Heidi Wouters, Liesbeth Heyns, Sileny N Han, Viktor Tomsk, Luc Martens, Petronella B Ottevanger

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Case control study on pediatric outcome after gestational cancer (n=129)

Pediatric Outcome after Maternal Cancer Diagnosed during Pregnancy

Pediatric Outcome after Maternal Cancer Diagnosed during Pregnancy

RISK FACTORS

After gestational chemotherapy, the kids are all right

Pedro A. Peccatori, Giacomo Corrado and Monica Fumagalli


When a pregnant woman is diagnosed with cancer, clinical management is complicated by concerns about the possible detrimental effects of cancer treatments on pregnancy outcome and the health of the baby. Evidence about the outcomes of children after maternal chemotherapy for cancer during pregnancy is growing and we can say 'the kids are all right'.

The clinical management of a pregnant woman who is diagnosed with cancer is complicated by concerns about the possible detrimental effects of oncological treatments on pregnancy outcome and the short-term and long-term health of the baby. Recent data have clarified that anthracyclines, taxanes, and platinum compounds have limited transplacental passage,¹ and when chemotherapy is administered to the pregnant woman after the first trimester, no increased risk of neonatal malformations has been described.² Nonetheless, concerns remain regarding the long-term health out-

“...treating pregnant women with chemotherapy during the second or third trimester is safe...”

Recently published papers have shed light on some of these issues. Teams of researchers from the USA,³,⁴ and Belgium⁵ have investigated the outcomes of children whose mothers had been treated with chemotherapy during pregnancy. In the study of Cardonick et al.,⁶ 35 children who were exposed to chemotherapy during pregnancy not jeopardize the health outcomes of the developing fetus. Importantly, however, the small sample size, the subjective nature of data acquisition (obtained through parent-administered questionnaires), and the short follow-up period in the study by Murthy et al.⁷ should be considered when interpreting results.

Amant et al.⁸ have investigated the long-term outcome of 70 children whose mothers received chemotherapy for various malignancies during pregnancy. The authors assessed children at birth, at 18 months of age, and at age 5–6, 8–9, 11–12, 14–15, or 18 years. They performed clinical neurological examinations, tests of the general level of cognitive functioning (Bayley or intelligence-quotient test), electrocardiography and echocardiography, and administered a questionnaire on general health and development. Moreover, from
Surgery for breast cancer during pregnancy

- Decision on type of surgery should follow standard practice anytime during pregnancy
- Mastectomy not mandatory, even in first trimester
- Careful anaesthesiological monitoring during surgery
- Breast reconstruction possible
- SLNB possible
- Adjuvant RT should be postponed after delivery
Immediate breast reconstruction with expander in pregnant breast cancer patients

Visnu Lohsiriwat a,b,1,2, Fedro Alessandro Peccatori c,*,1,3, Stefano Martella a,3, Hatem A. Azim Jr. c,2, Maria Anna Sarno c,2, Viviana Galimberti d,3, Francesca De Lorenzi a,3, Mattia Intra d,3, Claudia Sangalli e,3, Nicole Rotmensz f,2, Giancarlo Pruneri g,h,2, Giuseppe Renne g,2, Mario Casales Schorr a,3, Luiz Felipe Nevola Teixeira i,3, Mario Rietjens a,3, Massimo Giroda j,3, Oreste Gentilini d,3
Mean gestational age 16 w

10/12 axillary dissection

2/12 postmastectomy RT

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<th>Age</th>
<th>pT</th>
<th>pN</th>
<th>ER</th>
<th>HER2</th>
<th>Surgery</th>
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<th>Axillary node dissection</th>
<th>Radiotherapy</th>
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pT: pathological tumor size; pN: pathological nodal status; ER: estrogen receptor.
• Mean operative time 141 min (99-173)
• No maternal or fetal complications
• 75% completed inflation during pregnancy
• At a median FUP of 32 months 10/12 pts are NED
• 11 pts completed pregnancy, no fetal malformation
Axillary staging for breast cancer during pregnancy: feasibility and safety of sentinel lymph node biopsy

S. N. Han¹,¹³, F. Amant⁹,¹³, E. H. Cardonick²,¹³, S. Loibl¹,¹³, F. A. Peccatori⁴,¹³, O. Gheysens⁵,¹³, C. A. Sangalli³,¹³, V. Nekljudova³,¹³, K. Dahl Steffensen⁶,¹³, M. Mhallem Gziri⁷,¹³, C. P. Schröder⁸,¹³, C. A. R. Lok⁹,¹³, A. Verest¹,¹³, P. Neven¹,¹³, A. Smeets¹,¹³, G. Pruneri¹⁰,¹³, M. Cremonesi¹¹,¹³, O. Gentilini¹²,¹³. On behalf of the International Network on Cancer, Infertility and Pregnancy
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<tr>
<td>-99m TC albumin nanocolloid only</td>
<td>96 (66%)</td>
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<td>-Blue dye only</td>
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<td>-Combined</td>
<td>15 (10%)</td>
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<tr>
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<td>20 (14%)</td>
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<td><strong>Successful mapping</strong></td>
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<td><strong>Mean number of SLN</strong></td>
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<td><strong>Positive SLN</strong></td>
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<td><strong>Loco regional events at median FU: 48m</strong></td>
<td>11 (7%) (only 1 case of axillary recurrence)</td>
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<td><strong>Neonatal adverse events</strong></td>
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Take Home messages

• Multidisciplinarity !!!
Take Home messages

• Accurate staging without ionizing radiations (DW-MRI)
• Radiotherapy: usually contraindicated, unless fields are far from uterus
• Chemotherapy: contraindicated in first trimester, can be given starting W14 until W34-35
• The kids are all right, but premature delivery should be avoided
• Breast surgery during pregnancy not different from non-pregnant patients
Thank you!

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