PREGNANCY AND FERTILITY ISSUES IN BREAST CANCER PATIENTS

Fedro Peccatori, MD PhD
European Institute of Oncology,
European School of Oncology
Milan, Italy
CONFLICT OF INTEREST DISCLOSURE

✓ Personal financial interests: I received honoraria in the last 5 years from Roche, Astra Zeneca, Clovis, Takeda, Ipsen, PrIME Oncology

✓ Non-financial interests: I am active member of ASCO, ESMO, AIOM and ESGO

✓ Other: I act as Scientific Director of the European School of Oncology (ESO)
Fertility concerns of breast cancer patients

47% of young patients with breast cancer want a baby
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

73% concerned about fertility

57% seriously concerned about sterility

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

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

- Age at diagnosis > 35 years (mostly)
- Treatment chemo +/- prolonged hormonal Rx high
- Fear of pregnancy
Attitudes on fertility issues in breast cancer patients: an Italian survey

Nicoletta Biglia¹*, Rosalba Torrisi²*, Marta D’Alonzo¹*, Giovanni Codacci Pisanelli³, Selene Rota², and Fedro Alessandro Peccatori³

¹Department of Gynaecology and Obstetrics, University of Turin, Turin, Italy, ²Department of Hematology and Oncology, Humanitas Cancer Center, Milan, Italy, and ³Fertility and Procreation Unit, Division of Gynecologic Oncology, European Institute of Oncology (IEO), Milan, Italy
10. May a pregnancy in women previously affected by BCa increase the risk of recurrence?

Only 51% of oncologists believed that pregnancy does not affect the prognosis of BCa patients, while 49% of them supports that an increase in estrogen levels during pregnancy could stimulate the growth of hidden tumor cells (Statement 10).
Safety of pregnancy following breast cancer diagnosis: A meta-analysis of 14 studies

Hatem A. Azim Jr., Luigi Santoro, Nicholas Paulidis, Shari Gelber, Niels Kroman, Hamdy Azim, Fedro A. Peccatori
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 of pregnancy following breast cancer diagnosis: A meta-analysis of 14 studies

Hatem A. Azim Jr. a,b, Luigi Santoro c, Nicholas Paulidis d, Shari Gelber c, Niels Kroman Hamdy Azim b, Fedro A. Peccatori k.
Safety: meta-analysis

Studies corrected for “healthy mother effect”, 15% risk reduction

<table>
<thead>
<tr>
<th>Recurrence-free</th>
<th>No. of deaths/ No. of participants</th>
<th>Pregnant</th>
<th>Non-pregnant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mignot, 1986</td>
<td>10/68</td>
<td>21/136</td>
<td></td>
</tr>
<tr>
<td>Velentagas, 2000</td>
<td>5/53</td>
<td>34/265</td>
<td></td>
</tr>
<tr>
<td>Gelber, 2001</td>
<td>11/94</td>
<td>35/188</td>
<td></td>
</tr>
<tr>
<td>Kroman, 2008</td>
<td>46/199</td>
<td>3397/10037</td>
<td></td>
</tr>
</tbody>
</table>

Subtotal PRR (95% CI) 0.85 (0.53-1.35)

Q test for Heterogeneity p=0.31 P=15.4

<table>
<thead>
<tr>
<th>“Mortality”-free</th>
<th>No. of deaths/ No. of participants</th>
<th>Pregnant</th>
<th>Non-pregnant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cooper, 1970</td>
<td>7/28</td>
<td>22/56</td>
<td></td>
</tr>
<tr>
<td>Ariel, 1989</td>
<td>14/46</td>
<td>321/900</td>
<td></td>
</tr>
<tr>
<td>Sankila, 1994</td>
<td>8/91</td>
<td>145/471</td>
<td></td>
</tr>
<tr>
<td>Malamos, 1996</td>
<td>NR/21</td>
<td>NR/222</td>
<td></td>
</tr>
<tr>
<td>Lethaby, 1996</td>
<td>5/14</td>
<td>153/334</td>
<td></td>
</tr>
<tr>
<td>Birgisson, 2000</td>
<td>5/14</td>
<td>22/33</td>
<td></td>
</tr>
<tr>
<td>Blakely, 2003</td>
<td>10/47</td>
<td>147/323</td>
<td></td>
</tr>
<tr>
<td>Ives, 2007</td>
<td>NR/123</td>
<td>NR/2416</td>
<td></td>
</tr>
<tr>
<td>Largillier, 2009</td>
<td>6/118</td>
<td>222/762</td>
<td></td>
</tr>
</tbody>
</table>

Subtotal PRR (95% CI) 0.56 (0.44-0.70)

Q test for Heterogeneity p=0.02 P=54.0

Between-strata Heterogeneity: Meta-regression P-value=0.038

Relative Risk (95% Confidence Interval)
Prognostic Impact of Pregnancy After Breast Cancer According to Estrogen Receptor Status: A Multicenter Retrospective Study

Hatem A. Azim Jr, Niels Kroman, Marianne Paesmans, Shari Gelber, Nicole Rotmensz, Lieveke Ameye, Leticia De Mattos-Arruda, Barbara Pistilli, Alvaro Pinto, Maj-Britt Jensen, Octavi Cordoba, Evandro de Azambuja, Aron Goldhirsch, Martine J. Piccart, and Fedro A. Peccatori
Safety: multicenter study
In ER+ and ER- patients

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+

HR 0.91 (95% CI 0.67-1.24)
Safety: DFS in ER-

HR 0.75 (95% CI 0.51-1.08)
Safety: OS in whole population

HR 0.72 (95% CI 0.54-0.97)
BRIEF COMMUNICATION

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

Safety: Long-term follow-up

DFS in ER+ cohort / median follow up 7.2 years

![Graph showing disease-free survival comparison between non-pregnant and pregnant cohorts over time.](Image)
Safety: Long-term follow-up

OS in ER+ cohort / median follow up 7.2 years

![Graph showing overall survival rates over time for nonpregnant and pregnant cohorts.](image-url)
Pregnancy following breast cancer using assisted reproduction and its effect on long-term outcome

Oranite Goldrat\textsuperscript{a, b}, Niels Kroman\textsuperscript{c}, Fedro A. Peccatori\textsuperscript{d}, Octavi Cordoba\textsuperscript{e}, Barbara Pistilli\textsuperscript{f}, Oejvind Lidegaard\textsuperscript{g}, Isabelle Demeestere\textsuperscript{b}, Hatem A. Azim Jr.\textsuperscript{h,*}
Table 3
Long-term survival outcome.

<table>
<thead>
<tr>
<th></th>
<th>Spontaneous pregnancy group, N = 173 (%)</th>
<th>ART pregnancy group, N = 25 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Interval diagnosis-last clinical FU (mo)</td>
<td>107</td>
<td>102</td>
</tr>
<tr>
<td>Interquartile range</td>
<td>81–131</td>
<td>85–123</td>
</tr>
<tr>
<td>Interval conception-last clinical FU (mo)</td>
<td>63</td>
<td>50</td>
</tr>
<tr>
<td>Interquartile range</td>
<td>37–89</td>
<td>27–72</td>
</tr>
<tr>
<td>Cancer related events (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Local recurrence</td>
<td>28 (16)</td>
<td>2 (8)</td>
</tr>
<tr>
<td>Distant recurrence</td>
<td>8 (4.6)</td>
<td>0</td>
</tr>
<tr>
<td>Contralateral breast cancer</td>
<td>10 (5.7)</td>
<td>2 (8)</td>
</tr>
<tr>
<td>2nd primary cancer (non-breast)</td>
<td>7 (4)</td>
<td>0</td>
</tr>
<tr>
<td>Death (n)</td>
<td>3 (1.7)</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>11 (6.3)</td>
<td>1 (4)</td>
</tr>
</tbody>
</table>

ART, assisted reproductive technology; FU, follow-up; mo, months.
What women want to know

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

CRITICAL FACTORS:

- Drugs administered (schedule and dosage)
- Age at diagnosis (oocyte quantity and quality)
- 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
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)
### Ovarian toxicity

*Panel 1: Estimated risk of gonadal dysfunction with cytotoxic drugs*\(^{29}\)

<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>
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</tr>
</tbody>
</table>
Human Ovarian Reserve from Conception to the Menopause

W. Hamish B. Wallace¹, Thomas W. Kelsey²

ESMO

Istituto Europeo di Oncologia
Ovarian reserve at chemo

Human Ovarian Reserve from Conception to the Menopause

W. Hamish B. Wallace, Thomas W. Kelsey
Ovarian reserve after chemo

Human Ovarian Reserve from Conception to the Menopause

W. Hamish B. Wallace, Thomas W. Kelsey
Ovarian reserve after chemo

Human Ovarian Reserve from Conception to the Menopause

W. Hamish B. Wallace, Thomas W. Kelsey
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 LHRHα during chemotherapy
1) Inform the patient about the risk of infertility

Young women desiring future fertility should be counselled on available fertility preserving options before starting anticancer treatments. Counselling should be implemented soon after diagnosis, to allow prompt referral to fertility specialists [IV, B]. Age is the most important determinant of chemotherapy or radiotherapy-induced ovarian dysfunction.
Inform the patient about the risk of infertility
2) Early referral

ID: initial diagnosis, FPC: fertility preservation counseling, BS: breast surgery, OS/OR: ovarian stimulation/oocyte retrieval
Early referral

ID: initial diagnosis, FPC: fertility preservation counseling
BS: breast surgery, OS/OR: ovarian stimulation/oocyte retrieval
3) Consider egg/embryo freezing before chemo

Gonadotrophin administration
Oocytes pick up

Oocytes freezing

IVF/ICSI and embryo freezing
Oocyte cryopreservation

John K. Jain, M.D., and Richard J. Paulson, M.D.

Department of Obstetrics and Gynecology, Division of Reproductive Endocrinology and Infertility, University of Southern California Keck School of Medicine, Los Angeles, California

Success rates of selected recently reported series using slow-freeze and vitrification methods.

<table>
<thead>
<tr>
<th>Author (y; reference no.)</th>
<th>Method</th>
<th>Survival rate, n (%)</th>
<th>Fertilization rate, n (%)</th>
<th>No. of oocytes per pregnancy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fabbri (2001 [35])</td>
<td>Slow-freeze</td>
<td>796/1,502 (53)</td>
<td>632/796 (79)</td>
<td>94</td>
</tr>
<tr>
<td>Chen (2005 [36])</td>
<td>Slow-freeze</td>
<td>119/159 (75)</td>
<td>80/119 (67)</td>
<td>23</td>
</tr>
<tr>
<td>Boldt (2006 [46])</td>
<td>Slow-freeze (sodium depleted)</td>
<td>218/361 (60)</td>
<td>134/218 (61)</td>
<td>26</td>
</tr>
<tr>
<td>Yoon (2003 [56])</td>
<td>Vitrification</td>
<td>325/474 (68.6)</td>
<td>142/198 (71.7)</td>
<td>79</td>
</tr>
<tr>
<td>Kuwayama (2005 [58])</td>
<td>Vitrification</td>
<td>58/64 (91)</td>
<td>52/58 (90)</td>
<td>5</td>
</tr>
</tbody>
</table>

* Cryopreserved and thawed cumulus–oocyte complexes.

90% vitality and fertilization rate after thawing 8-12 frozen oocytes - 30% probability of a baby
Consider egg/embryo freezing before chemo

ISSUES RELATED TO OVARIAN STIMULATION

✓ Safety (high estrogen levels)
✓ Efficacy (does it work)
✓ Timing (when to start ovarian stimulation)
Fig 1. Protocol for ovarian stimulation with letrozole and gonadotropins in patients diagnosed with breast carcinoma. In this regimen, letrozole is initiated on the second day of menstrual cycle and gonadotropins are started 2 days later. A gonadotropin-releasing hormone (GnRH) antagonist is administered when estradiol levels reach ≥ 250 pg/mL or the lead follicle size reaches 14 mm. Human chorionic gonadotropin (hCG) is administered when the leading follicle reaches 19 to 20 mm in diameter. Letrozole treatment is restarted after oocyte retrieval until the estradiol levels are lower than 50 pg/mL. FSH, follicle-stimulating hormone;
Safety: Controlled ovarian stimulation

Median FU 2 years

No. of patients at risk
Letrozole 79 74 37 18 7 5
Control 136 81 56 38 26 19

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 Kutluk Oktay

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

Long-Term Safety of Letrozole and Gonadotropin Stimulation for Fertility Preservation in Women With Breast Cancer

Jayeon Kim, Volkan Turan, and Kutluk Oktay

DOI: http://dx.doi.org/10.1210/jc.2015-3878
Safety: Controlled ovarian stimulation

ER+ with FP=98
ER- with FP=22

Long-Term Safety of Letrozole and Gonadotropin Stimulation for Fertility Preservation in Women With Breast Cancer

Jayeon Kim, Volkan Turan, and Kutluğ Oktay

DOI: http://dx.doi.org/10.1210/jc.2015-3878
Safety: Controlled ovarian stimulation

FP pre-surgery = 14
FP post-surgery = 106
Safety: Controlled ovarian stimulation

MULTICENTRIC REGISTRY-BASED COHORT STUDY (SWE)

Kaplan-Meier survival estimates

At risk after year:
- No FP: 351, 211, 88, 33, 10
- FP Not Hormonal: 38, 23, 10, 1, 0
- FP - Hormonal: 145, 61, 18, 0, 0

Adjusted Survival Curves
Efficacy: Controlled ovarian stimulation

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
Efficacy: Controlled ovarian stimulation

Peak estradiol levels 58.4-1.166 pg/ml (mean 405.94 \( \pm \) 256.64 pg/ml)

Average number of oocytes retrieved \( 10.3 \pm 7.75 \)

Average number of frozen embryos \( 5.97 \pm 4.97 \)

10 embryo implanted, 5 deliveries.

Mean age at procedure \( 36.1y \ (SD \ 3.8) \)
Efficacy: Controlled ovarian stimulation

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)

- 9 deliveries
- 11 children born

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

- Underwent FET once (n = 8)
  - 6 deliveries
  - 10 children born

- Underwent FET twice (n = 7)
  - 3 deliveries
  - 4 children born

FET: frozen embryo transfer

Fertility Preservation Success Subsequent to Concurrent Aromatase Inhibitor Treatment and Ovarian Stimulation in Women With Breast Cancer

Kutluk Oktay, Volkan Turan, Giuliano Bedoschi, Fernanda S. Pacheco, and Fred Moy

VOLUME 33 · NUMBER 22 · AUGUST 1 2015
Timing: Random start ovarian stimulation

Random-start gonadotropin-releasing hormone (GnRH) antagonist–treated cycles with GnRH agonist trigger for fertility preservation

Shweta R. Nayak, M.D., and Anthony N. Wakim, M.D.
Division of Reproductive Endocrinology and Infertility, Department of Obstetrics and Gynecology, University of Pittsburgh Medical Center, Pittsburgh, Pennsylvania

Objective: To describe our experience with random-start IVF with the use of GnRH agonist for final oocyte maturation, to reduce the risk of ovarian hyperstimulation syndrome.

Design: Case series.

Setting: University-based center for reproductive endocrinology and infertility.

Patient(s): Patients with a new diagnosis of cancer who presented with a narrow time frame for IVF before initiating cancer therapy.


Main Outcome Measure(s): Number of oocytes retrieved, fertilization rate, rates of ovarian hyperstimulation syndrome.

Results: Cycles were started in the late follicular or luteal phase, and the duration of controlled ovarian hyperstimulation ranged between 8-13 days. A total of 14-40 oocytes were retrieved and 5-20 embryos cryopreserved for each patient.

Conclusion(s): Random-start IVF is a reasonable option for fertility preservation in those cancer patients for whom the treatment window may be narrow. In addition, the use of a GnRH agonist for final oocyte maturation may decrease the potential risk of ovarian hyperstimulation syndrome. (Fertil Steril 2011;96:e51-4. ©2011 by American Society for Reproductive Medicine.)

Key Words: GnRH agonist, random-start IVF, fertility preservation

Effective method for emergency fertility preservation: random-start controlled ovarian stimulation

Hakan Cakmak, M.D., Audra Katz, R.N., Marcelle I. Cedars, M.D., and Mitchell P. Rosen, 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.

Patient(s): Women recently diagnosed with cancer and in preparation for gonadotoxic therapy.

Intervention(s): Random versus conventional-start COS.

Main Outcome Measure(s): Primary outcome: number of mature oocytes retrieved; secondary outcomes: 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-start (n = 35) and conventional-start (n = 93) COS cycles. No superiority was noted when comparing COS started in the late follicular (n = 13) or luteal phase (n = 22). The addition of letrozole, 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.

Conclusion(s): Random-start COS is as 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 2-3 weeks. (Fertil Steril 2013;100:1673-80. ©2013 by American Society for Reproductive Medicine.)

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

Discuss: You can discuss this article with its authors and with other ASRM members at http://www.fertstertforum.com/askmds-fertility-preservation-controlled-ovarian-stimulation/
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*

¹Department of Medical Oncology, U.O. Oncologia Medica 2, IRCCS AOU San Martino-IST, Genova; ²Unit of Clinical Epidemiology, IRCCS AOU San Martino-IST, Genova; ³Fertility and Procreation Unit, Gynecologic Oncology Department, European Institute of Oncology, Milan, Italy; ⁴BreAST Data Centre, Department of Medicine, Institut Jules Bordet, Université Libre de Bruxelles, Brussels, Belgium; ⁵Department of Internal Medicine, University of Genoa, Unit of Clinical Epidemiology, IRCCS AOU San Martino-IST, Genova, Italy; ⁶German Breast Group (GBG), Neu-Isenburg; ⁷Sana-Klinikum Offenbach, Offenbach am Main, Germany; ⁸Cleveland Clinic Foundation, Taussig Cancer Institute, Cleveland; ⁹Department of Medical Oncology, Dana-Farber Cancer Institute, Boston, USA; ¹⁰Department of Medical Oncology, U.O. Sviluppo Terapie Innovative, IRCCS AOU San Martino-IST, Genova, Italy

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

Gonadotropin-Releasing Hormone Agonists During Chemotherapy for Preservation of Ovarian Function and Fertility in Premenopausal Patients With Early Breast Cancer: A Systematic Review and Meta-Analysis of Individual Patient-Level Data


ABSTRACT

Purpose
The role of temporary ovarian suppression with gonadotropin-releasing hormone agonists (GnRHa) during chemotherapy as a strategy to preserve ovarian function and fertility in premenopausal women remains controversial. This systematic review and meta-analysis using individual patient-level data was conducted to better assess the efficacy and safety of this strategy in patients with early breast cancer.

Methods
The trials in which premenopausal women with early breast cancer were randomly assigned to receive (in)adjuvant chemotherapy alone or with concurrent GnRHa were eligible for inclusion. Primary endpoints were premature ovarian insufficiency (POI) rate and post-treatment pregnancy rate. Disease-free survival and overall survival were secondary endpoints. Because each study represents a cluster, statistical analyses were performed using a random-effects model.

Results
A total of 873 patients from five trials were included. POI rate was 14.1% in the GnRHa group and 30.0% in the control group (adjusted odds ratio, 0.38; 95% CI, 0.26 to 0.57; P < .001). A total of 27 (10.3%) patients had at least one post-treatment pregnancy in the GnRHa group and 20 (6.5%) in the control group (incidence rate ratio, 1.83; 95% CI, 1.06 to 3.15; P = .002). No significant differences in disease-free survival (adjusted hazard ratio, 1.01; 95% CI, 0.72 to 1.42; P = .859) and overall survival (adjusted hazard ratio, 0.67; 95% CI, 0.42 to 1.06; P = .080) were observed between groups.

Conclusion
Our findings provide evidence for the efficacy and safety of temporary ovarian suppression with GnRHa during chemotherapy as an available option to reduce the likelihood of chemotherapy-induced POI and potentially improve future fertility in premenopausal patients with early breast cancer.

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Fertility Preservation by Endocrine Suppression of Ovarian Function Using Gonadotropin-Releasing Hormone Agonists: The End of the Controversy?

Zeev Blumberg, Technion-Israel Institute of Technology, Haifa, Israel
See accompanying article doi:https://doi.org/10.1002/jco.26196

The odds of preserving gonad function after gonadotropin chemotherapy are significantly better for prepubertal girls than for boys. Although ovarian function has been preserved in most long-term female survivors treated prepubertally for lymphomas, but only in approximately half of the similarly treated adult premenopausal women, it is clinically logical to generate a temporary and reversible prepubertal milieu before and during the gonadotropin chemotherapy. Many groups of clinicians have been using gonadotropin-releasing hormone agonists (GnRHa) concent- ments for minimizing the gonadotoxic effects of chemotherapy, by stimulating a prepubertal hormonal milieu, with the rationale that preventing premature ovarian insufficiency (POI) is preferable to treating it. However, reported results addressing this strategy have been conflicting, and several major international guidelines still consider it experimental.

In the article that accompanies this editorial, Lamberini et al. have conducted a systematic review using individual patient-level data of randomized controlled trials (RCTs), meta-regression analysis, and a random-effects model to statistical analysis to evaluate the GnRHa strategy in patients with early breast cancer. This study provides robust evidence for both the efficacy and the safety of temporary ovarian suppression with GnRHa during chemotherapy as a noninvasive clinical option to reduce POI and improve future fertility. Their meta-analysis, including only well-conducted RCTs, supports the use of GnRHa to prevent POI and improve future fertility in patients with breast cancer. Considering that it is the first meta-analysis to specifically review the role of GnRHa in the prevention of POI in patients with breast cancer who receive chemotherapy, their findings are consistent with those of previous studies that included women with breast cancer and demonstrated a reduction in the risk of POI with GnRHa treatment. Therefore, GnRHa should be considered as a viable option for women undergoing chemotherapy who are at risk of developing POI.

The conclusions of the present study are consistent with previous findings from randomized controlled trials (RCTs) and observational studies that have demonstrated a reduction in the risk of POI with GnRHa treatment. The results of the present study suggest that GnRHa treatment may be an effective strategy for preventing POI in patients with breast cancer who receive chemotherapy. However, further research is needed to confirm these findings and determine the optimal timing and duration of GnRHa treatment.
POI rate

POI = premature ovarian insufficiency

OR* 0.38 (95% CI 0.26–0.57)

P<.001

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

GnRHa Group: 37/359 (10.3%)

Control Group: 20/367 (5.5%)

IRR* 1.83 (95% CI 1.06-3.15)

\[ P = .030 \]

<table>
<thead>
<tr>
<th>Age distribution, years</th>
<th>GnRHa Group</th>
<th>Control Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \leq 40 )</td>
<td>37 (100%)</td>
<td>20 (100%)</td>
</tr>
<tr>
<td>( \geq 41 )</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Estrogen receptor status</th>
<th>GnRHa Group</th>
<th>Control Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive</td>
<td>6 (16.2%)</td>
<td>2 (10.0%)</td>
</tr>
<tr>
<td>Negative</td>
<td>31 (83.8%)</td>
<td>18 (90.0%)</td>
</tr>
</tbody>
</table>

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

**Disease-Free Survival, %**

- **HR** *1.01 (95% CI 0.72–1.42) P = .999

**Overall Survival, %**

- **HR** *0.67 (95% CI 0.42–1.06) P = .083

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

IQR, interquartile range

Conclusions

Oncologists’ Role in Patient Fertility Care
A Call to Action

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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 preserve fertility and ovarian function.
THANK YOU!

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