Fertility preservation (in young females)

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ESMO PRECEPTORSHIP PROGRAMME
ADOLESCENT & YOUNG ADULT MALIGNANCIES
Lugano, 11-12 May 2018
Fertility preservation in young males is easy!
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(^a)</th>
<th>Type of Cancer</th>
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<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>Non-Hodgkin Lymphoma, n=169(^a)</td>
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<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>Breast Cancer, n=223</td>
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<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>Gastrointestinal Cancer, n=108</td>
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<tr>
<td>Children before treatment, No. (%)</td>
<td>476 (52%)</td>
<td>46 (38%)</td>
<td>105 (37%)</td>
<td>Non-Hodgkin Lymphoma, n=169(^a)</td>
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<td>Desiring children after treatment, No. (%)</td>
<td>504 (54%)</td>
<td>71 (59%)</td>
<td>181 (63%)</td>
<td>Breast Cancer, n=223</td>
</tr>
</tbody>
</table>

\(^a\) Numbers in parentheses are standard deviations.
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
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 cancer

Lambertini M, et al. Submitted to The Breast, 2018
Pregnancy rate after cancer: not all alike

Pregnancy rate varies according to tumor type

Analysis adjusted for education level, previous pregnancy age

Stensheim et al; Int J Cancer 2011
Pregnancy rate after cancer: not all alike

Worst rates for breast cancer: only 5-10% of subsequent pregnancies

Stensheim et al; Int J Cancer 2011
Pregnancy rate after cancer: not all alike

Best rates for melanoma: slight impact on subsequent pregnancies

Stensheim et al; Int J Cancer 2011
Breast cancer and impact on fertility

- Most frequent above 35 years
- High impact of adjuvant treatments
- Low awareness of fertility preservation
- High fear of pregnancy
Safety of pregnancy after breast cancer: 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 Paulidis 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 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, Pedro A. Peccatori h.
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 Pavlidis d, Shari Gelber e, Niels Kroman f, Hamdy Azim g, Pedro A. Peccatori h,*
Safety: multicenter study in ER+

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, nodal 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 elapsing between BC diagnosis and date of conception of the matched pregnant one. The primary objective was DFS in patients with 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) of 0.65.

Results
A total of 303 preg patients and 874 matched nonpregnant patients were analyzed, of whom 686 patients had an ER-positive disease. No difference in DFS was observed between pregnant and nonpregnant patients in the ER-positive HR = 0.91; 95% CI, 0.67 to 1.24, P = .55 or the ER-negative (HR = 0.76; 95% CI, 0.51 to 1.08, P = .12) cohorts. However, the pregnancy group had better OS HR = 0.72; 95% CI, 0.54 to 0.97, P = .03, with no interaction according to ER status (P = .11). 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.


INTRODUCTION

With advancements in local and systemic adjuvant therapies, there has been a continuous decline in recurrence rates and risk of death secondary to breast cancer (BC). This has led to more attention given to quality of life and survivorship issues, particularly for those diagnosed at a relatively young age. Over the past decade, there has been an increasing trend of women delaying childbearing. This has resulted in more patients with BC inquiring about fertility-related issues and whether a subsequent pregnancy could alter their risk of disease recurrence after completion of adjuvant therapy. Recent evidence suggests that 40% to 50% of women with history of BC may wish to have a subsequent pregnancy. However, only 4% to 7% manage to become pregnant, which emphasizes the need to improve the quality of available evidence to help counseling these women.

Recently, we conducted a large meta-analysis and found that pregnancy after BC diagnosis reduces the risk of death by 41%. However, this risk is likely confounded by a selection bias, known as the “healthy mother effect.” Indeed, patients who become subsequently pregnant are mostly patients with no evidence of relapse. Hence the improved outcome observed in the pregnant group could be a reflection of selecting nonsmoking patients and not due to the true effect of pregnancy on BC outcome.
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: multicenter study in ER+
Safety: long term follow-up (7.2 years)

DFS in ER+ patients

Disease-free survival, %

Time, y

Nonpregnant cohort
Pregnant cohort

No. at risk
Nonpregnant 492 346 233 134 32 5
Pregnant 194 138 88 50 17 4
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
Melanoma and impact on fertility

- Most frequent between 25 and 29 years
- Low impact of adjuvant treatments (?)
- Low awareness of fertility preservation
- High fear of subsequent pregnancy
966 women with pregnancy after melanoma

4567 women without pregnancy

Slightly thicker melanomas in the group without pregnancy (1.11 vs 0.82 mm vs P=0.003)

HR of death in women with subsequent pregnancy after melanoma: 0.58 (95% CI=0.32-1.05)
Safety of pregnancy after melanoma

Until now, the recommendation given to young female melanoma patients was to avoid pregnancies after the diagnosis of melanoma, particularly during the first 3 years after the diagnosis of the primary melanoma. This study provides no evidence to support deferral of pregnancy except that at the end of 3 years, patients have a better estimate of their risk of relapse. For patients with a good-prognosis thin tumor, in which the risk of relapse is small but changes comparatively little over time, there seems to be little justification at all for suggesting deferral.
What women want to know

What is the risk of treatment-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
**Panel 1: Estimated risk of gonadal dysfunction with cytotoxic drugs**

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<tr>
<th>High risk</th>
<th>Medium risk</th>
<th>Low risk</th>
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<tr>
<td>Cyclophosphamide</td>
<td>Cisplatin</td>
<td>Vincristine</td>
</tr>
<tr>
<td>Ifosfamide</td>
<td>Carboplatin</td>
<td>Methotrexate</td>
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<tr>
<td>Chlormethine</td>
<td>Doxorubicin</td>
<td>Dactinomycin</td>
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<tr>
<td>Busulfan</td>
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<td>Mercaptopurine</td>
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<tr>
<td>Procarbazine</td>
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<td>Vinblastine</td>
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<tr>
<td>Chlorambucil</td>
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Ovarian reserve

Menopause

Human Ovarian Reserve from Conception to the Menopause

W. Hamish B. Wallace, Thomas W. Kelsey
Ovarian reserve at chemotherapy

- Menopause
- CHEMOTHERAPY

Human Ovarian Reserve from Conception to the Menopause

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CHEMOTHERAPY

Menopause

Human Ovarian Reserve from Conception to the Menopause

W. Hamish B. Wallace, Thomas W. Kelsey

ESMO

IEO
Ovarian reserve estimation: AMH
Ovarian reserve estimation: AMH

Kelsey et al, 2011 PLOS
Treatment duration and ovarian ageing
Treatment duration and ovarian ageing
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 chemo (if breast cancer)
✓ Consider Ovarian Cortex Cryopreservation
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*

1Fertility and Procreation Unit, Division of Gynaecologic Oncology, European Institute of Oncology, Milan, Italy; 2Department of Medicine, Breast Data Centre, Institut Jules Bordet, Université Libre de Bruxelles, Brussels, Belgium; 3Department of Radiotherapy, European Institute of Oncology, Milan, Italy; 4Department of Surgical Oncology, University Medical Centre Groningen, Groningen, The Netherlands; 5Department of Medical Oncology, University of Ioannina, Ioannina, Greece; 6Department 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  ASCO SPECIAL ARTICLE

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

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

J Clin Oncol 36. © 2018 by American Society of Clinical Oncology

2013

2018
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 in breast cancer (Letrozole)
Safety: Controlled ovarian stimulation in breast cancer

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

Graphs showing the probability of reproductive success for ages 30-34 and 41-42, according to the 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., 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 (ICOS), in which a patient is stimulated on presentation regardless of her menstrual-cycle phase, has outcomes similar to conventional early follicular-phase start ICOS for fertility preservation in cancer patients.

Design: Retrospective cohort study.

Setting: Academic medical center.

Patients: Women recently diagnosed with and in preparation for gonadotoxic therapy.

Intervention: Random- versus conventional-start ICOS.

Main Outcome Measures: 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 (n = 35) and conventional-start (n = 93) ICOS cycles. No superiority was noted when comparing ICOS started in the late follicular (n = 13) or luteal phase (n = 28). The addition of letrozole, in the case of estrogen-sensitive cancers, did not adversely affect ICOS outcomes or oocyte maturity and competence in either random- or conventional-start protocols.

Conclusions: Random-start ICOS is an effective as conventional-start ICOS in fertility preservation. This protocol would minimize delays and allow more patients to undergo fertility preservation and still proceed with cancer treatment within 3-4 weeks. (Fertil Steril® 2011;96(6):1673-80. ©2013 by American Society for Reproductive Medicine.)

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

Discussion: You can discuss this article with its authors and with other ASRM members at http://ferdinforum.org/cakmak-fertility-preservation-controlled-ovarian-stimulation/

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

Volkan Turan, M.D.,** Giuliano Bedoschi, M.D.,** Fred Moy, Ph.D.,* and Kulthuk Oktay, M.D.*

* Innovation Institute for Fertility Preservation, New York, NY; Laboratory of Molecular Reproduction and Fertility Preservation, Obstetrics and Gynecology, New York Medical College, Valhalla, NY, and Biometrics, Data Management and PKPD 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 protocol for fertility preservation in breast cancer patients.

Design: Retrospective cohort study.

Setting: Academic fertility preservation center.

Patients: Seventy-eight women (45-65 years, diagnosed with stage I-III 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: Forty-one patients underwent single-cycle stimulation and 17 received two stimulation cycles. The mean total number of oocytes harvested (16.1 ± 13.2 vs. 19.6 ± 14.6) and embryos generated (6.4 ± 2.9 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 (13.7 ± 7.7 vs. 12.9 ± 13.0 days). A mean follow-up interval of 58 ± 13.6 months, the recurrence rates were similar between the two cycles (15 of 17) and single-cycle (1 of 49) 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;100:1651-8. ©2013 by American Society for Reproductive Medicine.)

Key Words: Breast cancer, consecutive cycles, fertility preservation, letrozole, ovarian stimulation

Discussion: You can discuss this article with its authors and with other ASRM members at http://ferdinforum.org/turan-ovarian-stimulation-letrzo-letrozole-fertility-preservation-breast-cancer/
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

<table>
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<th>Author</th>
<th>Odds Ratio (95% CI)</th>
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<th>Events, Controls</th>
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<td><strong>0.36 (0.23, 0.57)</strong></td>
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Favors LHRHa / Favors Controls

Lambertini et 2015, Annals of Oncology
Gonadotropin-Releasing Hormone Agonists During Chemotherapy for Preservation of Ovarian Function and Fertility in Premenopausal Women 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 no adjuvant chemotherapy alone or with concurrent GnRHa were eligible for inclusion. Primary and secondary endpoints were premature ovarian insufficiency (POI) rate and post-treatment pregnancy rate. Disease-free survival and overall survival were secondary end points. 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 30.9% in the control group (odds ratio, 0.38; 95% CI, 0.26 to 0.57; P < .001). A total of 47 (10.3%) patients had at least one post-treatment pregnancy in the GnRHa group and 15 (5.5%) in the control group (incidence rate, 1.83; 95% CI, 1.06 to 3.15; P = .030). No significant differences in disease-free survival (hazard ratio, 1.01; 95% CI, 0.72 to 1.42; P = .999) and overall survival (hazard ratio, 0.67; 95% CI, 0.42 to 1.06; P = .083) 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 chemotheray-induced POI and potentially improve future fertility in premenopausal patients with early breast cancer.

INTRODUCTION

Breast cancer is the most commonly diagnosed malignancy in premenopausal women, and its treatment often results in long-term sequelae and impaired quality of life. Given the improved prognosis of patients with breast cancer over the past years, survivorship issues are becoming more important. The use of anticancer therapies in premenopausal patients with breast cancer is associated with gonadotoxicity. Age of the patient at the time of treatment, type of chemotherapy regimen administered, and use of adjuvant endocrine therapy are crucial factors affecting the risk of developing this side effect. Chemotherapy-induced premature ovarian insufficiency (POI) can have a substantial negative impact on patients’ quality of life and is associated with several side effects, such as vasomotor symptoms, sexual dysfunction, and fertility-related problems.

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

Zeev Bramerfeld, Technion-Israel Institute of Technology, Haifa, Israel

See accompanying Editorial doi:10.1200/JCO.2018.76.0055

The odds of preserving gonadal function after gonadotropin therapy are significantly better for prepubertal girls than for boys. Although ovarian function has been preserved in most long-term female survivors treated prepuberally for lymphoma, but only in approximately half of the similarly treated adult reproductive-age women, it is clinically logical to generate a temporary and reversible prepuberal milieu before and during the gonadotropin therapy. Many groups of clinicians have been using gonadotropin-releasing hormone agonist (GnRHa) treatment for minimizing the gonadotoxic effects of chemotherapy. By simulating a prepuberal 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, Lamberti et al. have conducted a systematic review using individual patient-level data of randomized controlled trials (RCTs), multivariate logistic regression analysis, and a random effects model for analytical analyses to evaluate the GnRHa strategy in patients with early breast cancer. Their study provides robust evidence for both the efficacy and the safety of temporary ovarian suppression with GnRHa during chemotherapy as a non-invasive clinical option to reduce POI and improve fertility. In the main multivariate analysis, only GnRHa and young age were significantly associated with a reduced risk of POI and higher pregnancy rates in survivors, with comparable overall and disease-free survival. The authors should be congratulated for their scientific integrity and courage to re-evaluate their former conclusions, but comments should be made regarding the number of patients who have previously published analyses that did not support the efficacy of GnRHa.

The only prior meta-analysis that assessed the ovarian histology before and after GnRHa treatment along with chemotherapy (which obviously cannot be conducted in humans) was done 23 years ago. This prospective randomized study has demonstrated that GnRHa may protect the ovary against cyclophosphamide-induced gonadal damage. Since that time, 27 publications (12 RCTs, 23 non-RCTs, and 13 meta-analyses) have reported on 2,900 patients (1,551 in the RCTs) treated with GnRHa in parallel with chemotherapy, demonstrating a significant decrease in POI compared with studies including 569 patients that did not demonstrate efficacy. For several years, the pendulum has switched from positive to negative conclusions and back regarding the ability of GnRHa to minimize gonadotoxicity and preserve fertility. For the past few years, the pendulum movement tends toward a positive conclusion, possibly ending the debate and suggesting that GnRHa adjustment to menopause may indeed preserve ovarian function and fertility without an adverse effect on survival.

Four recent international consensus meetings support the use of GnRHa for fertility preservation. The 16th St Gallen International Consensus stated that GnRHa therapy during chemotherapy “proved effective to protect against POI and preserve fertility” and increased the rate of subsequent pregnancies without compromising disease outcomes. The second expert consensus, the National Comprehensive Cancer Network guidelines, summarized 18 recommendations, graded according to the levels of evidence (according to the European Society for Medical Oncology Clinical Practice Guidelines). The only conclusion that received the highest grade was the conclusion regarding GnRHa (“Ovarian suppression with GnRHa during chemotherapy should be considered a reliable strategy to preserve ovarian function and fertility, at least in breast cancer patients, given the availability of new data suggesting both the safety and the efficacy of the procedure…”).

The third and fourth international consensus meetings similarly concluded that GnRHa has beneficial roles in young patients with Hodgkin lymphoma and the survivors of breast cancer and hematopoietic–receptor–negative breast cancer. The conclusions of these four international expert meetings are in keeping with recent summaries and meta-analyses of RCTs, including the Cochrane collaboration analysis, confirming that the use of GnRHa was associated with a reduced risk of POI and significantly increased pregnancy rate. In addition, GnRHa can effectively prevent chemotherapy-associated menopausal symptoms. The Italian Association of Medical Oncologists decided to adopt the routine clinical use of temporary ovarian suppression with GnRHa during chemotherapy as a strategy to preserve ovarian function and fertility in patients with breast cancer.

The published dispute and controversy between the supporters of GnRHa and its opponents has occasionally been heated. Several papers may possibly explain the controversy, including the fact that short follow-up may lead to incorrect conclusions. Indeed, in their present study, Lamberti et al. did not find a significant difference in POI after 1 year, whereas in
**Premature-Ovarian Insufficiency Rate**

OR* 0.38 (95% CI 0.26–0.57)  
*P<.001*

<table>
<thead>
<tr>
<th>Study</th>
<th>GnRHa Group Events/pts</th>
<th>Control Group 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>
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<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%, <em>p</em> = 0.85)</td>
<td>37/359</td>
<td>20/367</td>
<td>1.82 (1.05, 3.14)</td>
</tr>
</tbody>
</table>

**Age distribution, years**

<table>
<thead>
<tr>
<th></th>
<th>GnRHa Group</th>
<th>Control Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤40</td>
<td>37 (100)</td>
<td>20 (100)</td>
</tr>
<tr>
<td>≥41</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
</tr>
</tbody>
</table>

**Estrogen receptor status**

<table>
<thead>
<tr>
<th></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>

**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)  
\( P = .999 \)

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

Consider ovarian cortex cryopreservation

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.1,2 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.6

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-
Thank you!

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