~1 in 51 women will suffer invasive cancer by age 39

Options for Fertility Preservation in Adolescents: GnRH Agonists or Not?

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University of Florida COM
Round Table Luncheon, April 7, 2016

According to ASCO, ESMO and ASRM guidelines published in 2013, GnRH analogs should not be relied upon as a fertility-preservation method (30, 32, 35).

ANTICANCER RESEARCH 35: 3117-3128 (2015)

Learning Objectives:

1. To define and discuss the options for fertility preservation in adolescents

2. To describe the fertility preservation options in pre-pubertal population

3. To evaluate and discuss the pros and cons of using GnRH agonists in adolescents with cancer and other serious medical conditions

Disclosures – None

Off Label Use – GnRH agonists
17 year old presents with newly diagnosed osteosarcoma. She is in high school but wants to have children in the future.

She is worried the medicines might cause her to be infertile or sterile.

What Are Her Options?

AWARENESS
**ASCO/AAP Guidelines**


- As part of informed consent prior to therapy, oncologists should address the possibility of infertility with patients
- Referral for interested patients to reproductive endocrinologists (REI)
- Discussion at the earliest possible opportunity
- Sperm, oocyte, and embryo cryopreservation are standard practices, other methods are investigational – only for centers with expertise

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**Oncological Indications:**

<table>
<thead>
<tr>
<th>Low risk subfertility (20%)</th>
<th>Medium risk</th>
<th>High risk subfertility (&gt;80%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALL</td>
<td>AML</td>
<td>Whole body RT</td>
</tr>
<tr>
<td>Wilm's tumor</td>
<td>Hepatoblastoma</td>
<td>Pelvic RT</td>
</tr>
<tr>
<td>Soft tissue sarcoma (I)</td>
<td>Osteosarcoma</td>
<td>Chemo for BMT</td>
</tr>
<tr>
<td>Germ cell tumor (No RT)</td>
<td>Ewing sarcoma II or III</td>
<td>Hodgkin's treated with alkylating agents</td>
</tr>
<tr>
<td>Retinoblastoma</td>
<td>NH-lymphoma</td>
<td>Sarcoma IV</td>
</tr>
<tr>
<td>Brain tumor</td>
<td>Hodgkin's ,alternating treatment</td>
<td>Metastatic Ewing Sarcoma</td>
</tr>
<tr>
<td>Brain tumor (RT)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BREAEST CANCER</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Non-oncological indications:

<table>
<thead>
<tr>
<th>BMT</th>
<th>Autoimmune requiring CT</th>
<th>Ovarian pathologies</th>
<th>Endocrine/genetic diseases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vasculitis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sickle cell anemia</td>
<td>SLE</td>
<td>Recurrent cysts</td>
<td>Turner syndrome</td>
</tr>
<tr>
<td>Thalassemia major</td>
<td>Rheumatoid arthritis</td>
<td>Torsion</td>
<td>Galactosemia</td>
</tr>
<tr>
<td>Aplastic anemia</td>
<td>Behcet's disease</td>
<td>Family hx of POF</td>
<td></td>
</tr>
<tr>
<td>Autoimmune dx</td>
<td>Wegener’s disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Multiple sclerosis</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Long Term Survivors Face

- Organ toxicity
- Secondary malignancies
- Impaired reproductive capacity/ acute ovarian failure (AOF) – diagnosis of infertility can be as devastating as disease diagnosis

Incidence of AOF in childhood cancer survivors - 6.3-12%, and even if ovarian function retained the risk of premature menopause is increased
Side Effects of Childhood Cancer Therapy

- Failure to enter puberty
- Temporary or permanent cessation of menstrual cycles
- Lack of female hormones
- Infertility
- Pregnancy risks
- Bone loss if low estrogen or early onset heart disease

What types of cancer therapy increase the risk of ovarian failure?

- Radiation therapy to any of the following areas:
  - Whole abdomen
  - Pelvis
  - Lower spine (buttocks and sacral areas)
  - Total body (TBI)
  - Head/neck (external)—if dose was 10 Gy (100 Gy) or higher

- Chemotherapy—The class of drugs called alkylators can cause ovarian failure when given in high doses. Examples of these drugs are:
  - Alkylation agents:
    - Busulfan
    - Cisplatin (CDDP)
    - Chlorambucil
    - Cyclophosphamide (Cytoxan®)
    - Bleomycin
    - Lomustine (CCNU)
    - Mechlorethamine (nitrogen mustard)
    - Melphalan
    - Procarbazine
    - Thiopeta
  - Heavy metals:
    - Cisplatin
    - Carboplatin
  - Non-classical alkylators:
    - Dacarbazine (DTIC)
    - Teniposide
  - Surgery:
    - Removal of one or both ovaries
Prevention of chemotherapy-induced ovarian damage: possible roles for hormonal and non-hormonal attenuating agents

Potential Uses of AMH in Women With Rheumatic Disease/Cancer
(Helping women make a reproductive life plan)

- To measure ovarian protection by GnRH agonist cotherapy
- Measure AMH before CYC therapy to guide immunosuppressant choice and ovarian preservation methods
- To guide family planning in women with cancer/rheumatic disease

Clowse et al, 2012
AMH Overview

Anti-Mullerian Hormone (AMH)

- Produced in granulosa cells
- Assess ovarian aging
- Predict response to gonadotropins
- Assess risk for OHSS
- Help diagnose PCOS

- Earliest marker to change with age
- Least intercycle variability
- Least intracycle variability
- Random blood draw

AMH best marker of ovarian reserve pre/post therapy, better than FSH and menstrual cyclicity

Fertil Steril(99):6,May 2013, 1469-1475
Ovarian Reserve Testing
Antral Follicle Count (AFC)

Gonadal Protection for Children Undergoing Chemotherapy
Infertility represents one of the main long-term consequences of chemotherapy. Studies that evaluated the effects of ovarian suppression by GnRHs during chemotherapy in adult and adolescent patients have yielded inconsistent results. Prospective, randomized trials in adult women are ongoing (see NCT00196846, NCT0090844, NCT00380406, NCT0068601 at http://clinicaltrials.gov/).

Conclusions: Routine use of GnRHs for gonadal protection in children undergoing chemotherapy cannot be suggested (CIII).

PEDIATRICS Volume 123, Number 4, April 2009
GnRH Analog Coadministration During Chemotherapy

The American Society of Clinical Oncology does not recommend analog coadministration as a standard method for fertility preservation; still its use causes menstrual suppression and protection from thrombocytopenia. Therefore, it can be beneficial, but not for fertility-sparing. Depending on this approach for fertility preservation raises ethical issues.

OBSTETRICS & GYNECOLOGY
VOL. 126, NO. 1, JULY 2015

Options for Pre-pubertal FP
(* = experimental)

Male
- Testicular Tissue cryopreservation*
- Spermatogonial stem cell transplantation*
- Shielding testis from radiation

Female
- Immature oocyte cryopreservation and IVM*
- Ovarian tissue cryopreservation*
- Ovarian transposition

<table>
<thead>
<tr>
<th>Options for FP post-pubertal</th>
<th>(* = experimental)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Male</strong></td>
<td><strong>Female</strong></td>
</tr>
<tr>
<td>• Semen cryopreservation</td>
<td>• Oocyte cryopreservation</td>
</tr>
<tr>
<td></td>
<td>• Embryo cryopreservation</td>
</tr>
<tr>
<td></td>
<td>• Ovarian tissue cryopreservation*</td>
</tr>
<tr>
<td></td>
<td>• GnRH analogs*</td>
</tr>
</tbody>
</table>

**Mature Oocyte Cryopreservation – A Guideline**

- There is good evidence that fertilization and pregnancy rates are similar to IVF/ICSI with fresh oocytes when vitrified/warmed oocytes are used as part of IVF/ICSI for young women. Although data are limited, no increase in chromosomal abnormalities, birth defects, and developmental deficits has been reported in the offspring born from cryopreserved oocytes when compared to pregnancies from conventional IVF/ICSI and the general population.

- Evidence indicates that oocyte vitrification and warming should no longer be considered experimental.

_Fertility and Sterility 2012_
Oocyte Cryopreservation

Must be well enough
Need oncology clearance

- Harvest and freeze unfertilized eggs
- After puberty
- 1000’s of live births worldwide
- Live birth rate ~ 4.5 -12% per egg
- Better in women under 38

PROVEN

Egg Freezing

Advantages:
- No male partner needed
- Avoids ethical dilemmas of freezing embryos
- Proven effectiveness

Disadvantages:
- Oocytes more sensitive to freezing, due to high lipid content, large volume, and spindle in cell
- Cost
- Need for ovarian stimulation
- Delay of chemotherapy
Ovarian Tissue Cryopreservation

- Ovary removed or strips of cortex, laparoscopically, divided into small strips, frozen and stored
- Before or after puberty
- **Experimental**, with > 60 live births
- 1000's of pieces frozen
- Re-implantation may restore hormone function temporarily and progress puberty
- Not suitable if high risk of ovarian mets such as leukemia, ovarian tumors, or with very ill patient

*Large number of immature oocytes in ovarian cortex, so may be combined with freezing immature oocytes*

Fertil Steril,99(6), 2013:1503-1513  
Fertil Steril,99(6), 2013:1514-1521

- Transplantation of thawed cryopreserved ovarian tissue, post chemotherapy
- LSC removal of ovarian cortical strip for freezing before chemotherapy

Usually temporary recovery due to accelerated follicular loss

Fertil Steril May 2013
GnRH Analog Treatment

- Administer before chemotherapy initiated, at least one week before
- After puberty
- Experimental, with various study results

Blumefeld et al, Fertil Steril, 2008; 166-173
Clowse et al, J of Women's Health, 2009; 311-319
Beck-Fruchter et al, Human Reprod Update, 2008; 555-561

Clinical Indications For GNRH Agonist

- Endometriosis
- Central precocious puberty
- Uterine Fibroids
- Dysfunctional uterine bleeding
- Premenstrual syndrome
- Assisted reproduction
- Fertility preservation?
Is There A Biological Basis For GNRH FP Action?

- Do primordial follicles express GnRH receptors?
- Does GnRH interfere with follicular apoptosis mechanisms?
- If it interferes with cell death, does it lessen the effectiveness of chemotherapy induced cell death?
- FINALLY – Does using GnRH interfere with using other proven methods?

Consensus Statement on the Use of Gonadotropin-Releasing Hormone Analogs in Children

<table>
<thead>
<tr>
<th>TABLE 3 Depot GnRH Formulations</th>
<th>STARTING Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Depot Preparation</strong></td>
<td><strong>Brand Name</strong></td>
</tr>
<tr>
<td>Goserein</td>
<td>Zoladex LA</td>
</tr>
<tr>
<td>Buserelin</td>
<td>Suprefact depot</td>
</tr>
<tr>
<td>Leuprolide</td>
<td>Enantone or Lupron-depot</td>
</tr>
<tr>
<td></td>
<td>Prostap SR</td>
</tr>
<tr>
<td></td>
<td>Lupron depot PED</td>
</tr>
<tr>
<td>Triptorelin</td>
<td>Decapeptyl</td>
</tr>
<tr>
<td></td>
<td>Gonapeptyl</td>
</tr>
<tr>
<td>Mestrelin</td>
<td>Supprelin LA</td>
</tr>
</tbody>
</table>

* No data are available on the use of the 22.5-mg 3-month depot in children.
Use of GnRH Agonists and FP

<table>
<thead>
<tr>
<th>Trial</th>
<th>Population</th>
<th>Intervention</th>
<th>Follow-up</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>ZIPP, 2009</td>
<td>Breast CA</td>
<td>Gosorelin</td>
<td>36 mos</td>
<td>P = .006</td>
</tr>
<tr>
<td>Badawy, 2009</td>
<td>Breast CA</td>
<td>Gosorelin</td>
<td>6 mos</td>
<td>P &lt; .001</td>
</tr>
<tr>
<td>ZORO, 2011</td>
<td>Breast CA</td>
<td>Gosorelin</td>
<td>24 mos</td>
<td>P = .28</td>
</tr>
<tr>
<td>Promise, 2011</td>
<td>Breast CA</td>
<td>Triptorelin</td>
<td>12 mos</td>
<td>P &lt; .001</td>
</tr>
<tr>
<td>Munster, 2012</td>
<td>Breast CA</td>
<td>Triptorelin</td>
<td>18 mos</td>
<td>P = .16</td>
</tr>
</tbody>
</table>

Bottom Line – Potential Benefit, but Not Established Yet!

McLaren JF and Bates MG, 2012

TABLE 1: Characteristics of GnRhAg

<table>
<thead>
<tr>
<th>Rapid Acting</th>
<th>Monthly Depot</th>
<th>3-mo Depot</th>
<th>12-mo Implant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dosage</td>
<td>3-times daily transdermal or every day subcutaneously</td>
<td>Every 3 wk</td>
<td>Every 3 mo</td>
</tr>
<tr>
<td>Peak serum concentrations</td>
<td>10-25 ng/ml</td>
<td>48 h</td>
<td>48 h</td>
</tr>
<tr>
<td>Onset of therapeutic suppression</td>
<td>2-4 wk</td>
<td>1 mo</td>
<td>1 mo</td>
</tr>
<tr>
<td>Advantage</td>
<td>Quick onset</td>
<td>Dosing and efficacy well studied</td>
<td>Fewer injections and fewer compliance concerns</td>
</tr>
<tr>
<td>Disadvantage</td>
<td>Multiple daily doses needed/ compliance very difficult</td>
<td>Painful injections/suboptimal compliance</td>
<td>Painful injection</td>
</tr>
</tbody>
</table>

PEDIATRICS Volume 123, Number 4, April 2009

Consensus Statement on the Use of Gonadotropin-Releasing Hormone Analogs in Children
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

OR for ovarian failure

<table>
<thead>
<tr>
<th>Author</th>
<th>OR (95% CI)</th>
<th>Events Treated</th>
<th>Events control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bayley (2006)</td>
<td>0.34 (0.24, 0.49)</td>
<td>1086</td>
<td>2794</td>
</tr>
<tr>
<td>Osterlind (2009)</td>
<td>0.39 (0.39, 0.55)</td>
<td>1264</td>
<td>3141</td>
</tr>
<tr>
<td>Caruso (2013)</td>
<td>0.28 (0.22, 0.37)</td>
<td>4010</td>
<td>5766</td>
</tr>
<tr>
<td>Li et al. (2010)</td>
<td>0.28 (0.22, 0.37)</td>
<td>4010</td>
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<td>4010</td>
<td>5766</td>
</tr>
</tbody>
</table>

Figure 4. Odds ratios for pregnancy ovarian failure by study definition, of patients treated with ovarian suppression using luteinizing hormone-releasing hormone agonists. The squares on the oval are plotted proportional to the weight of each study. CI: confidence interval; OR: odds ratio.
### 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

#### OR for pregnancy

<table>
<thead>
<tr>
<th>Author</th>
<th>Odds ratio (95% CI)</th>
<th>Events</th>
<th>Odds ratio (95% CI)</th>
<th>Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lerman et al. (2014)</td>
<td>2.60 (0.94, 7.22)</td>
<td>8/150</td>
<td>2.10 (0.76, 5.65)</td>
<td>2/100</td>
</tr>
<tr>
<td>Gider et al. (2011)</td>
<td>1.95 (0.95, 2.43)</td>
<td>10/19</td>
<td>1.00 (0.43, 2.30)</td>
<td>1/10</td>
</tr>
<tr>
<td>Maceira et al. (2015)</td>
<td>0.75 (0.51, 1.12)</td>
<td>4/26</td>
<td>0.75 (0.46, 1.25)</td>
<td>4/26</td>
</tr>
<tr>
<td>Elderly 1 (2015)</td>
<td>1.20 (0.46, 3.23)</td>
<td>12/51</td>
<td>1.20 (0.46, 3.23)</td>
<td>12/51</td>
</tr>
<tr>
<td>Elderly 2 (2015)</td>
<td>3.32 (1.31, 8.33)</td>
<td>10/35</td>
<td>3.32 (1.31, 8.33)</td>
<td>10/35</td>
</tr>
<tr>
<td>More (2016)</td>
<td>2.23 (1.04, 4.77)</td>
<td>20/50</td>
<td>2.23 (1.04, 4.77)</td>
<td>20/50</td>
</tr>
</tbody>
</table>

**Figure 4.** Odds ratio for women with pregnancy compared patients treated with gonadotropin-releasing hormone agonists (GnRHa) versus those treated with chemotherapy alone (C). The squares on the odds ratio plot are proportional to the weight of each study (GnRHa, luteinizing hormone-releasing hormone agonists, C, chemotherapy).


### Utility of gonadotropin-releasing hormone agonists for prevention of chemotherapy-induced ovarian damage in premenopausal women with breast cancer: a systematic review and meta-analysis

#### Study or subgroup

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Chemotherapy + GnRHa</th>
<th>Chemotherapy alone</th>
<th>Weight</th>
<th>Odds ratio (95% CI)</th>
<th>Odds ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>26 events</td>
<td>25 events</td>
<td>0.25</td>
<td>1.41 (1.02, 1.94)</td>
<td>1.19 (0.80, 1.76)</td>
</tr>
<tr>
<td>Gider et al.</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>1.00 (0.36, 2.80)</td>
<td>1.00 (0.36, 2.80)</td>
</tr>
<tr>
<td>Maceira et al.</td>
<td>22</td>
<td>19</td>
<td>12</td>
<td>0.89 (0.56, 1.42)</td>
<td>0.89 (0.56, 1.42)</td>
</tr>
<tr>
<td>Elderly 1</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>1.00 (0.41, 2.42)</td>
<td>1.00 (0.41, 2.42)</td>
</tr>
<tr>
<td>Elderly 2</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>1.00 (0.41, 2.42)</td>
<td>1.00 (0.41, 2.42)</td>
</tr>
<tr>
<td>More</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>1.00 (0.41, 2.42)</td>
<td>1.00 (0.41, 2.42)</td>
</tr>
<tr>
<td>Total</td>
<td>26 events</td>
<td>25 events</td>
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<td>1.41 (1.02, 1.94)</td>
<td>1.19 (0.80, 1.76)</td>
</tr>
</tbody>
</table>

**Figure 3.** Forest plot of the rate of spontaneous pregnancy for GnRHa agonists plus chemotherapy versus chemotherapy alone in a fixed-effect model. Abbreviations: CI, confidence interval; GnRHa, gonadotropin-releasing hormone agonists; MT, Menopausal.

*OncoTargets and Therapy* 2015:8
GnRH Agonist Side Effect Profiles

Figure 3 Forest plot of the ratio of event rates for GnRH agonists plus chemotherapy versus chemotherapy alone in a random-effect model.

Abbreviations: CI, confidence interval; GnRH, gonadotropin-releasing hormone; HR, Hazard Ratio.

OncoTargets and Therapy 2015:8
Options for Prevention and Management of Heavy Menstrual Bleeding in Adolescents undergoing Cancer Treatment (20 cases/100,000/year)

- Caused by myelosuppression and thrombocytopenia
- Disruption of hypothalamic – pituitary – ovarian axis causing anovulatory bleeding
- Tailor therapy to patient, her cancer diagnosis, her treatment plan, desire for contraception and future fertility
- Coordinate care with her oncologist

ACOG Committee Opinion, # 606, August 2014

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Options for Prevention and Management of Heavy Menstrual Bleeding in Adolescents undergoing Cancer Treatment

- Progestin only pills
- Combined oral contraceptives
- Progestin IUD
- GnRH agonists – Leuprolide acetate* (3.75-7.5mg IM monthly to 11.25-22.5mg IM q 3 months)

Lower risk of thromboembolism

Fertility preservation?

Side effects

ACOG Committee Opinion, # 606, August 2014
Hormones During Hematopoietic Cell Transplant

Prior to transplant evaluation:
- Review of medical history
- Review of fertility history
- Review of contraceptive history
- Review of current hormone use
- Review of current contraception
- Review of current medication use
- Review of current gynecologic examination
- Review of current menstrual status

When to consider gynecologic risk:
- Review of current hormone use
- Review of current contraception
- Review of current gynecologic examination
- Review of current menstrual status

Hormonal options for menstrual suppression and contraception at the time of transplant:

Prophylactic gynecologic examination

Pros
- Injectable
- Contraceptive benefit
- Stops menses
- Fertility preservation +

Cons
- Expensive
- Unproven for FP
- Hot flashes
- Vaginal Dryness
- Mood swings
- Bone loss with prolonged use
- Worsen depression
- Possible flare

Fig. 1: Hormonal treatment options for therapeutic amenorrhea and contraception. *Copper intrauterine devices (IUDs) should be removed. Laminaria-based IUDs may be continued or removed after discussion among the patient, transplant team, and gynecology team. The patient can be counseled that removal may be requested if she develops neutropenic fever during transplant.

The End Result!

Or For Kids and Families, The Choice

Concluding Remarks/Thoughts Questions
Resources For Information

- Livestrong/Fertile Hope – A national nonprofit organization providing reproductive information, support (often financial) and hope to cancer patients and survivors whose medical treatments present the risk of infertility.

- ASCO’s website – http://www.asco.org

- MyOncofertility.org (for patients and physicians – 24 hour phone hotline)