Updates on Fertility Preservation

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UF HEALTH HOPE NETWORK

(HELPING ONCOLOGY PATIENTS BECOME EDUCATED)

FLASCO 2023

Learning Objectives

- To review current options for oncofertility and benign fertility preservation
- Identify clinical situations where fertility preservation is indicated and the benefits of offering this to cancer patients

Definitions

Fertility Preservation:

- Preserving reproductive ability due to fertility altering therapies for benign conditions or for social reasons

Oncofertility:

- Preserving reproductive ability before cancer treatments that could alter fertility

Fertility Matters

Improved quality of cancer care had resulted in improved outcomes and higher rates of survival

Increased importance of addressing late effects of treatment and long term quality of life issues

Fertility Matters

- Fertility Preservation has been cited as one of the top five unmet needs for adolescent cancer patients- some reporting the decision regarding fertility preservation almost as distressing as the cancer battle
- Studies show that AYA patients would like to be informed of the effects of cancer treatment on their fertility as well as be educated about fertility preservation options
- Patients expect these conversations to happen as early as possible and with a reproductive specialist knowledgeable in risk assessments and fertility preservation options
- Fertility consults improve quality of life and may lead to less decisional regret once treatment is complete

Kelvin, J., et al. Journal of Clinical Oncology. 2016; 34: 1780-1786; Anazodo, A., et al. Human Reproduction Update; 2019; 25: 159-179

Fertility Preservation Guidelines

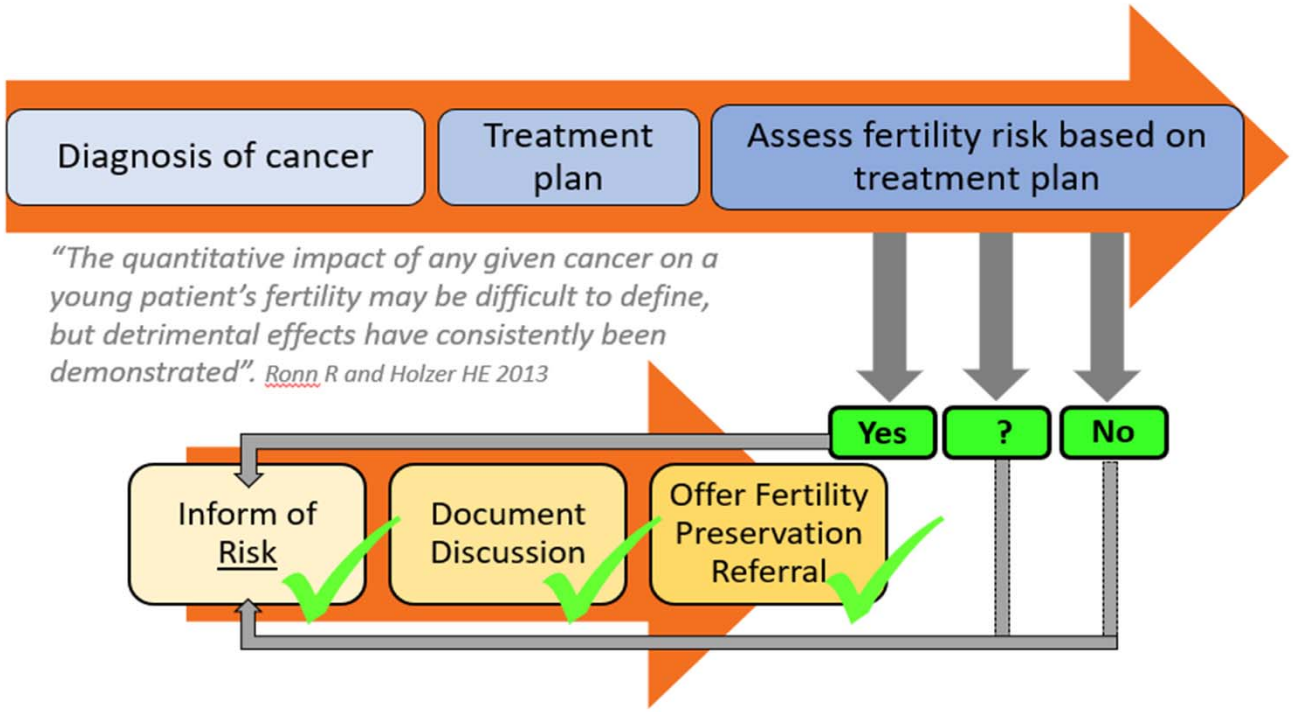
ASCO

ASRM

AAP

Health Care providers should inform patients of potential risks to fertility as a result of treatment, discuss fertility preservation options and refer interested patients to reproductive specialists prior to gonadotoxic chemotherapy

Fertility Preservation Guidelines



ASCO Fertility Preservation Guidelines 2018; Fertile Hope 2008; Oncofertility Consortium; Ronn R and Holzer HE 2013, Curr Oncol 2013 Aug;20(4):e338-44

Despite this….

Fertility Preservation care remains underutilized

Barriers to Fertility Preservation

Provider issues	• Personal biases/presumptions/assumptions • Knowledge gaps
Safety concerns	• Hormones used for ovarian hyperstimulation • Treatment delay
Ethical concerns	• Uncertain prognosis • Treatment of minors • Experimental procedures
Logistical issues	• Access to established fertility centers • Difficult referral pathways/limited providers
Financial issues	• Expensive • Not covered by insurance
Institutional and societal issues	• Lack of collaboration and communication • Lack of state/nation wide mandates for coverage of fertility preservation

Quinn GP, et al. J Cancer Surviv. 2007;1:146–155; Chong AL, et al Pediatr Blood Cancer. 2010;55:1356–1361; Kim J, et al Fertil Steril. 2012;97:671–676.

How do we address these barriers?

Fertility Preservation Program

- Increases fertility referrals
- Increases fertility preservation procedures
- Increases the rate of documented patient- provider conversations about fertility preservation

Vu, J., et al. Journal Surgical Oncology. 2017; 115: 116-121

Fertility Preservation Program

- Streamline referral processes
- Use decision aids to help educate patients
- Provide written and verbal education
- Document discussions
- Involve allied health professionals

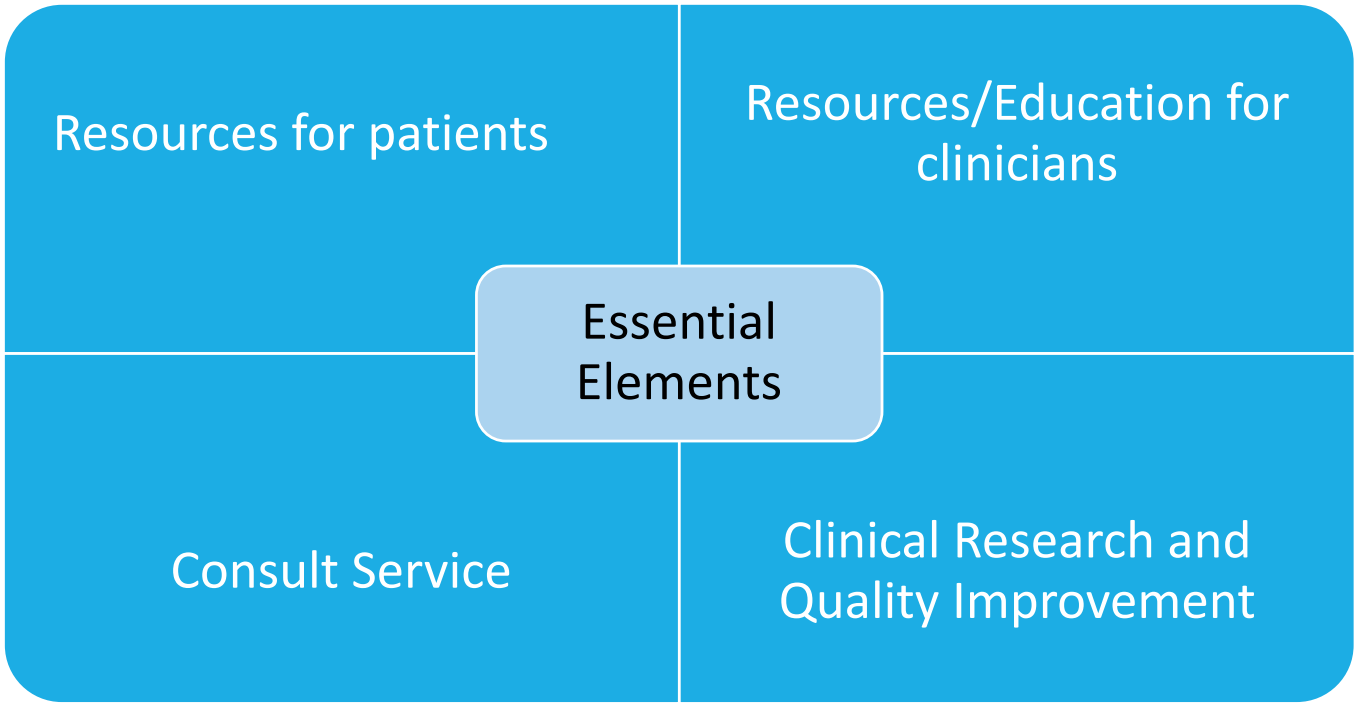
  Bedside/clinic nurses, social workers, Child Life Specialists, Psychologists, PA/ARNPs

Anazodo, A. et al. Human Reproductive Update, 2019; 25 (2): 159-179; Quinn, G. et al, Journal of Adolescent and Young Adult Onc. 2016, 5(3): 292-296

Essential Members of Fertility Preservation Team

Moravek, M, et al. Journal of Adolescent Health, 2019; 64: 563-573

Fertility Preservation Program

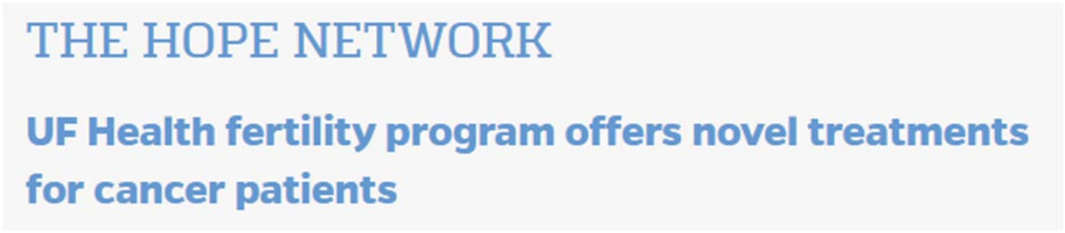


Kelvin, J., et al. Journal of Clinical Oncology. 2016; 34: 1780-1786

HOPE NETWORK- *Helping Oncology Patients Become Educated*

UF Health has established the HOPE Network- a formal oncofertility program

Program provides inpatient and outpatient consults for newly diagnosed oncology patients, rheumatology patients, patients undergoing stem cell transplant and patients desiring fertility preservation for benign/social reasons



HOPE NETWORK- *Helping Oncology Patients Become Educated*

- **Alice Rhoton-Vlasak, Director REI**
- **Stan Williams, REI**
- **Lauren Staley , Inpatient nurse navigator**
- **Jaime Williams – REI clinical nurse liaison**
- **Joe Kramer –REI embryology/ lab director**
- **Nash Moawad, MIGS surgeon**
- **Joanne Lagmay- AYA Program Director**
- **Patricia Durning –Clinical psychologist**
- **Climb for Cancer Foundation – Grant funding partners for clinical and educational programs**
- **Pruitt Family Foundation**

Oncofertility Training

Training Program for Health Professionals in Communication about Reproductive Health

ECHO

Enriching
Communicaton Skills
for
Health Professionals in
Oncofertility

What is ECHO?

ECHO is web-based training program that includes psychosocial, biological, clinical and skill building modules to help oncology health professionals communicate timely and relevant information regarding reproductive health to their adolescent and young adult (AYA) patients. **This program and course materials are provided at no cost to participants.**

Key ENRICH Participation Benefits:

- Training facilitated by a national team of experts
- Certificate of completion
- Educational materials
- **$150.00 stipend**
- Develop expertise in discussing cancer related reproductive health issues

How to Nominate/Apply:

Please go to RHOinstitute.org or email ECHO@Moffitt.org to submit an application request or your nomination. Applicants will need to submit the following no later than **January 31, 2017**.

- Application
- Personal Statement

Who is Eligible?

Registered nurses, licensed clinical psychologists, social workers, and physician assistants in the oncology care setting who provide care for at least five AYA patients a year.

What Will be Needed to Participate?

- Complete all modules and course requirements at your own pace during the 8 week training period
- Have access to a computer with Internet
- Complete periodic assessments/evaluations

Training Topics Include Improved Communication Skills in:

- Male and female reproductive health
- Pediatric psychosocial development
- AYA sexual health
- AYA psychosocial development
- Reproductive health communication skills
- Overcomming system barriers to reproductive health discussions and referrals

Training Activities Include:

- Lectures
- Case studies
- Discussion boards
- Video vignettes

For additional information or questions, please contact us at: (813)745-6941 • ECHO@Moffitt.org •RHOinstitute.org

Who can we see?

Non Oncologic Indications:

BMT	Autoimmune requiring CT	Ovarian pathologies	Endocrine/genetic alterations
	Vasculitis		
Sickle cell anemia	SLE	Recurrent cysts	Turner syndrome
Thalassemia major	Rheumatoid arthritis	Torsion	Galactosemia
Aplastic anemia	Behcet's disease	Endometriosis	Family hx of POF
Autoimmune dx	Wegener's disease		Transgender care
	Multiple sclerosis		

Social Reasons –Planned Egg Freezing

Oncologic Indications:

Low risk subfertility (20%)	Medium risk	High risk subfertility (>80%)
ALL	AML	Whole body RT
Wilm's tumor	Hepatoblastoma	Pelvic RT
Soft tissue sarcoma (I)	Osteosarcoma	Chemo for BMT
Germ cell tumor (No RT)	BREAST CANCER	Hodgkin's treated with alkylating agents
Retinoblastoma	NH-lymphoma	Sarcoma IV
Brain tumor	Hodgkin's ,alternating treatment	Metastatic Ewing Sarcoma
	Brain tumor (RT)	

MALES	Treatment	Cancer
High **>80%** risk of prolonged azoospermia	TBI Testicular XRT ≥ 2.5Gy men ≥ 6Gy boys Protocols with Procarbazine Alkylators for conditioning Alkylators + XRT (TBI/pelvic/testicular) Cyclophosphamide >7.5G/m^2 Cranial/Brain XRT ≥ 40Gy	SCT Testicular cancer, testicular leukemia/lymphoma Hodgkin SCT SCT, sarcoma, ALL, NHL, Hodgkin Sarcoma, neuroblastoma, ALL Brain tumors
Intermediate **20-80%** risk of prolonged azoospermia	BEP 2-4 cycles Cisplatin < 400 mg/m^2 Testicular XRT 1-6Gy (scatter)	Testicular cancer OSA (480 mg/m^2) Testicular cancer Wilms, Neuroblastoma
Low **<20%** risk of prolonged azoospermia	Non-alkylating chemo Testicular XRT 0.2-0.7Gy	Hodgkin, NHL Testicular cancer
No Risk Negligible effect on spermatogenesis	Testicular XRT <0.2Gy Interferon Radioactive iodine	Multiple Multiple Thyroid cancer
Unknown risk	Irinotecan Bevacizumab (VEGF-) Cetuximab (EGFR-) Erlotinib (EGFR2-) Imatinib (TKI)	Sarcomas, colon CA Colon, NSC Lung CA Colon, Head/Neck NSC Lung CA, pancreatic CML, GIST

FEMALES	Treatment	Cancer
High **>80%** risk of prolonged amenorrhea	Whole abdominal/pelvic XRT ≥6Gy women ≥10Gy post-pubertal ≥15Gy pre-pubertal TBI CMF/CEF/CAF x6 cycles ≥ 40y Cyclophosphamide 5G/m^2 ≥40y Cyclophosphamide 7.5G/m^2 <20y Alkylators for conditioning Protocols with Procarbazine Alkylators + XRT (TBI/pelvic/testicular) Cranial/Brain XRT ≥ 40Gy	 Multiple Wilms, neuroblastoma, sarcoma, Hodgkin SCT BRCA Multiple Sarcoma, neuroblastoma, NHL, ALL SCT Hodgkin SCT, sarcoma, ovarian CA, Hodgkin, neuroblastoma Brain tumor
Intermediate **20-80%** risk of prolonged amenorrhea	CMF/CEF/CAF x6 cycles 30-39y AC ≥ 40y Whole abdomen/pelvic XRT 10-15Gy prepubertal 5-10Gy post pubertal Spinal XRT ≥25Gy	BRCA BRCA Wilms, neuroblastoma Spinal tumors, brain tumor, neuroblastoma, relapsed ALL/NHLAC
Low **<20%** risk of prolonged amenorrhea	AC 30-39y CMF/CEF/CAF x6 cycles <30y Non-alkylating chemo (ABVD/CHOP, COP) Anthracycline Cytarabine	BRCA BRCA Hodgkin, NHL, ALL AML AML
No risk Negligible effect on menses	MTX/5FU VCR Radioactive iodine	BRCA Multiple Thyroid CA
Unknown	Taxanes Oxaliplatin Trastuzumab (HER2-) Irinotecan Bevacizumab (VEGF-) Cetuximab (EGFR-) Erlotinib (EGFR2-) Imatinib (TKI)	BRCA, sarcoma Ovarian CA BRCA Sarcomas, colon CA Colon, NSC Lung CA Colon, Head/Neck NSC Lung CA, pancreatic CML, GIST

Options for Pre-pubertal FP

*= experimental

Male: (WE HAVE IRB)

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

Female:

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

Options for Post-pubertal FP

*= experimental

Male:

- Semen cryopreservation

Female:

- Oocyte cryopreservation
- Embryo cryopreservation
- Ovarian tissue cryopreservation
- GnRH analogs*
- Chemoprotective agents – such as MTOR inhibitors*

Sperm Cryopresevation and Banking (Post Pubertal Male)

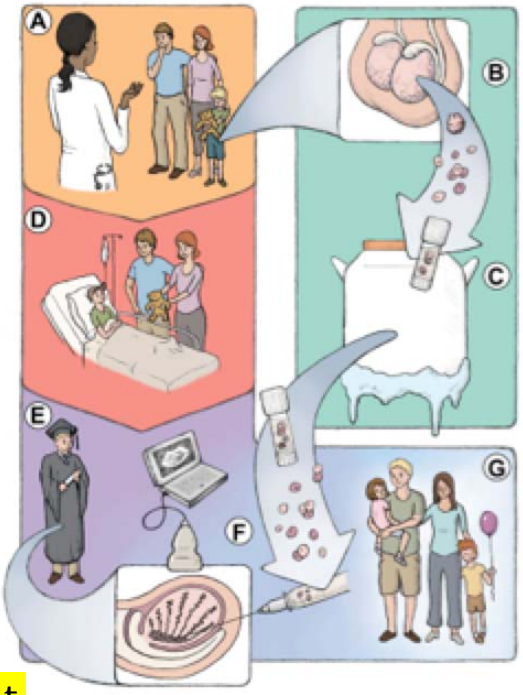
- Freezing sperm obtained through masturbation
- May remain frozen indefinitely
- Sperm counts may be low or absent as a result of cancer
- Use in future with intrauterine insemination or IVF
- Cost ~900$ including storage fees - **CFC funds for consult fees**

Azospermia found in 9.7-17.3% of males referred for banking;
11.9% of men died, 80% within 30 mos

KIM ET AL, FERTIL STERIL 2009; 2349-2354

Testicular Tissue Cryopreservation

- **Experimental,** no live births to date-**Before or after puberty**
- Outpatient – need IRB prepubertal
- Urologic procedure
- Requires in vitro sperm maturation or germ-cell transplantation
- Requires reproductive urologist – we have one
- University of Pittsburg – Kyle Orwig



Front Pediatr. 2022; 10: 909000.
Published online 2022 Sep 6. doi: 10.3389/fped.2022.909000

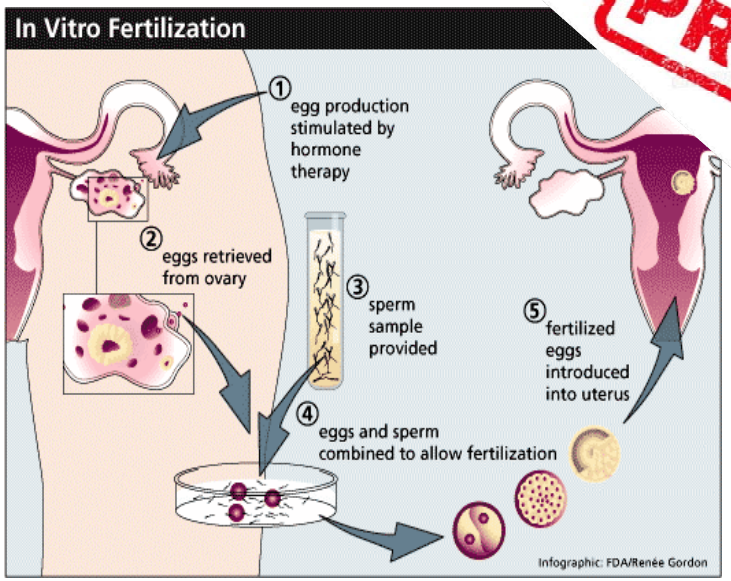
Testicular tissue cryopreservation for fertility preservation in prepubertal and adolescent boys: A 6 year experience from a Swiss multi-center network

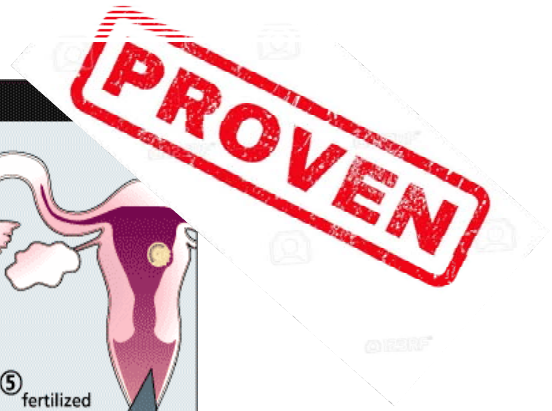
Donor Sperm

- Usually anonymous
- Done if no options available and patient rendered sterile
- Use with female partners eggs for IUI or IVF
- Good success rates

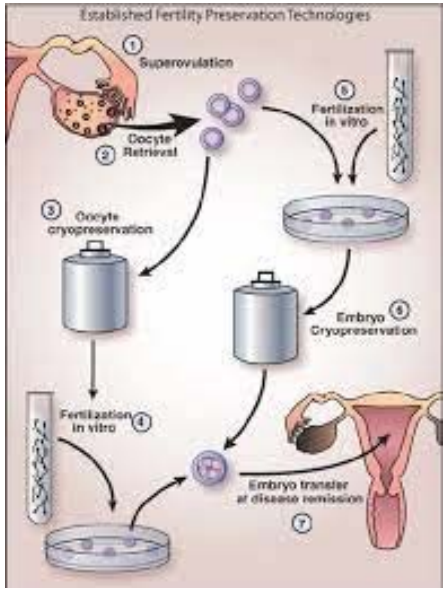
Embryo Banking (Post-Pubertal Females)

- ASCO recommendation
- Standard IVF
- Mature eggs removed, fertilized with sperm, frozen and stored
- After puberty
- 2-3 weeks required
- What to do about partner?





Oocyte Cryopreservation (Post-pubertal Female)



- Harvest and freeze unfertilized eggs
- Thawed in future to fertilize, make embryos and do transfer
- Better in women under 38

Problems in Adolescents: Timing/Delays; Need for sedation anesthesia; Discomfort with vaginal scans

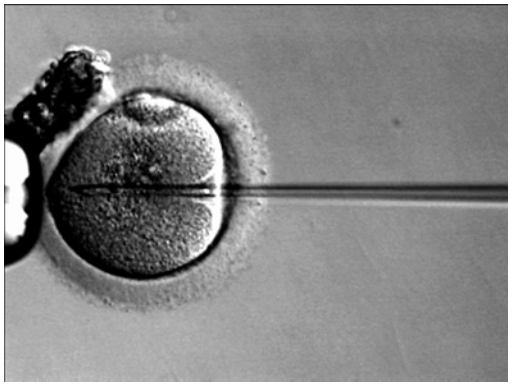
Oocyte Cryopreservation (post-pubertal female)

Advantages:

- No male partner needed
- Avoids ethical dilemmas of freezing embryos

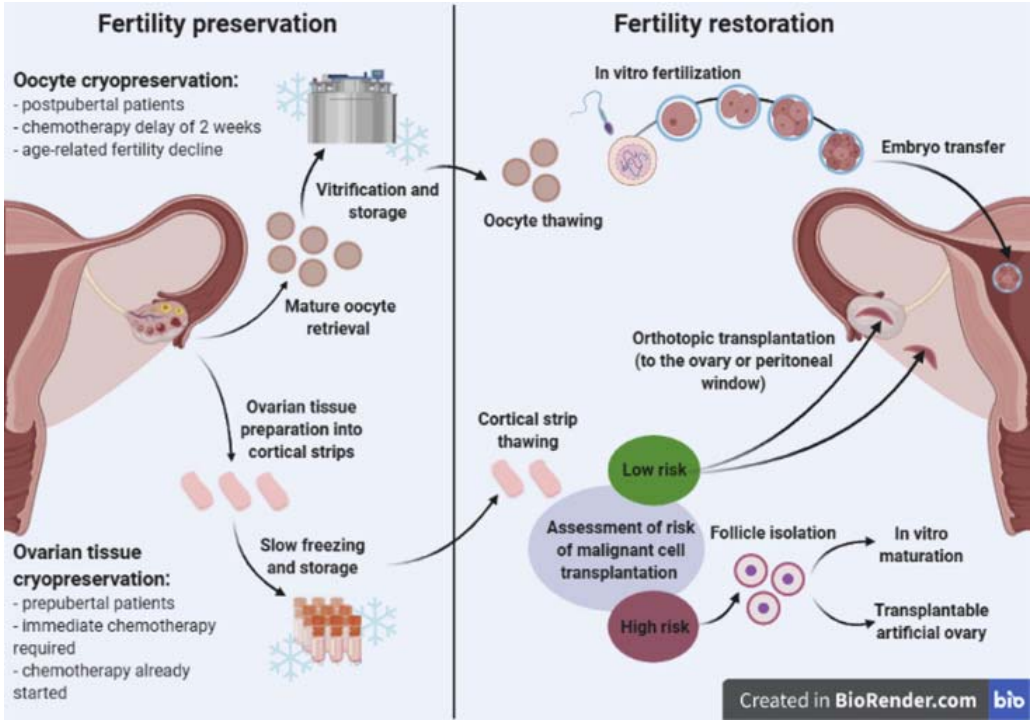
Disadvantages:

- Oocytes more sensitive to freezing, due to high lipid content, large volume, and spindle in cell



Ovarian Tissue Cryopreservation

- Ovary removed or strips of cortex, laparoscopically, divided into small strips, frozen and stored
- Before or after puberty (IRB for birth-40)
- **Experimental in pre-pubescent females**
- 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**



Transplantation of thawed cryopreserved ovarian tissue, post chemotherapy

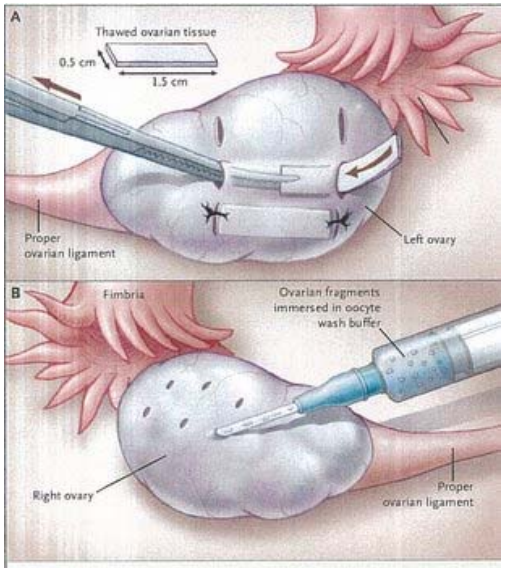
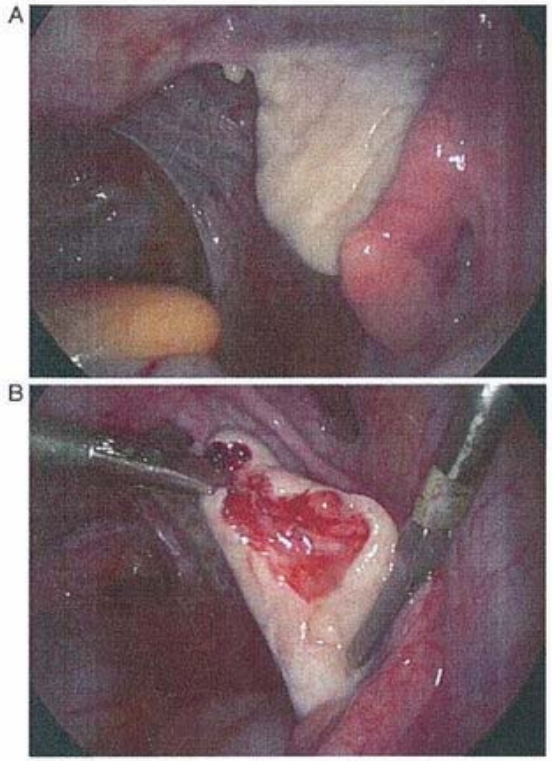


Figure 2. Surgical Technique.
Three pairs of 5-mm transverse incisions were made in the left ovary through the tunica albuginea (Panel A). With blunt dissection, cavities were formed beneath the cortex for each of the three strips. Each piece of thawed ovarian tissue (1.5 by 0.5 cm in area and 0.1 to 0.2 cm in thickness) was gently placed in a cavity, and the incisions were closed with 4/0 Vicryl sutures. In the smaller, right ovary, tiny ovarian fragments immersed in oocyte wash buffer were injected beneath the cortex (Panel B). Only the ovarian strips placed in the left ovary resumed function.

LSC removal of ovarian cortical strip for freezing before chemotherapy



Transplantation of cryopreserved ovarian tissue in a series of 285 women: a review of five leading European centers

Table 1 Pregnancy outcomes and age of women undergoing frozen-thawed OTT followed by natural conception or IVF.

Method of conception	Women undergoing OTT	Women wishing to conceive	Women who conceived[a]	Women who gave birth	Miscarriages	No. of children[b]	Age (y) at OTC of women who gave birth—mean ± SEM (range)	Age (y) at OTC of women who did not give birth—mean ± SEM (range)
Women conceiving naturally	176	167 (100%)	67 (40%)	52 (30%)	18 (10%)	67	27.6 ± 0.8[c] (17–36)	29.7 ± 0.6[c] (10–44)
Women undergoing IVF	109	109 (100%)	39 (36%)	23 (21%)	20 (18%)	28	25.1 ± 1.2[d] (9–33)	29.9 ± 0.6[d] (17–39)
Total	285	276 (100%)	106 (38%)	75 (26%)	38 (13%)	95	26.9 ± 0.7[e] (9–36)	29.8 ± 0.4[e] (10–44)

IVF = in vitro fertilization; OTC = ovarian tissue cryopreservation; OTT = ovarian tissue transplantation; SEM = standard error of the mean.

a Some women may have become pregnant and suffered a miscarriage before a successful subsequent pregnancy, explaining why "women who gave birth" plus "miscarriages" does not add up to "women who conceived."

b Some women became pregnant more than once after OTT or had a twin pregnancy.

c $P = .046$.

d $P = .0002$.

e $P = .0005$ (Student's *t*-test).

DOLMANS ET AL FERTIL STERIL ,VOLUME 115, ISSUE 5, P1102-1115, MAY 01, 2021

Pros and Cons:

Egg cryopreservation

- More cost effective
- Less surgery
- Slightly higher PR
- Will not restore hormones if menopausal
- Only post pubertal

TABLE 3

Efficiency of oocyte vitrification and ovarian cortex cryopreservation in fertility preservation.

OV	Patients (n = 49)
Warmed oocyte/patient	5.1 (3.5)
Oocyte survival rate, %	77.3
No. of ET (fresh-frozen)	68
Surplus embryos/patient	2.7 (2.2)
Warmed embryo/patient	2.0 (1.7)
Embryo survival rate, %	91.7
No. of embryos transferred	1.42
CPR/fresh cycle (%)	14/51 (27.4)
LBR/fresh cycle (%)	11/51 (21.6)
CPR/transfer (%)	20/55 (36.4)
LBR/transfer (%)	16/55 (29.1)
No. of pregnancies	21 (42.9)
No. of live births	17 (34.7)
No. of pregnant patients	20 (40.8)
No. of patients with live births	16 (32.6)
OCT	**Patients, n = 44 (%)**
Surgical approach	
Laparoscopy	1 (2.3)
Laparotomy	41 (93.2)
Surgical technique/sites	
Subcortical pouches	24 (54.5)
Cortical microsurgical sutures	26 (59.1)
Subperitoneal pouches	27 (61.4)
Ovarian function after graft	43 (97.7)
CPR after spontaneous pregnancy	7 (15.9)
LBR after spontaneous pregnancy	5 (11.4)
No. of patients undergoing IVF	28
CPR after IVF	8 (18.2)
LBR after IVF	5 (11.4)

Note: Values of quantitative variables are shown as mean (standard deviation) and values of categorical variables are shown as n (%). CPR = clinical pregnancy rate; ET = embryo transfer; LBR = live-birth rate; OCT = ovarian cortex cryopreservation and transplantation; OV = oocyte vitrification.

Diaz-Garcia. Fertility after oocyte vitrification and ovarian transplantation. Fertil Steril 2017.

GnRH Analog Treatment (Post-pubertal female)

- Administer monthly before chemotherapy initiated, at least one week before
- Can also prevent heavy menstrual bleeding with thrombocyopenia
- Experimental, with various study results

OFF LABEL USE

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; 553-561

GnRH Analog Treatment (Post-pubertal female)

CHILDREN'S ONCOLOGY GROUP

The world's childhood cancer experts

Guideline for Fertility Preservation for Patients with Cancer

3.5 Ovarian suppression: There is conflicting evidence to recommend GnRHa and other means of ovarian suppression for fertility preservation. The Panel recognizes that, when proven fertility preservation methods such as oocyte, embryo, or ovarian tissue cryopreservation are not feasible, and in the setting of young women with breast cancer, GnRHa may be offered to patients in the hope of reducing the likelihood of chemotherapy-induced ovarian insufficiency. However, GnRHa should not be used in place of proven fertility preservation methods.

2022

ID	Title	Trial design	Age range (years)	Number of estimated patients (disease)	Arms and interventions	Outcome measures	Follow-up duration
NCT02856048	Co-treatment With GnRH Analogs on the Ovarian Reserve in Young Women Treated With Alkylating Agents for Cancer (PRESOV Study), Sponsor Assistance Publique-Hôpitaux de Paris	Phase II/III randomized open-label	12–25	160 (Ewing Sarcoma, Osteosarcoma, Lymphoma)	1. Triptorelin 3 mg i.m. every 28 ± 3 days + Chemotherapy with alkylating agents at an intermediate ovarian toxicity risk* 2. Chemotherapy alone	Variation in AMH serum levels at 24 months; AFC on ultrasound at 24 months; delay of resumption of menses; AMH, FSH, estradiol levels monitoring; pregnancy rate at 3 years; GnRH-related AEs; change in BMD at 12 and 36 months	3 years
NCT04536467 (actual completion date June 1th 2020)	Prevention of Chemotherapy-Induced Ovarian Failure With Goserelin in Premenopausal Lymphoma Patients, Sponsor Beni-Suef University	Phase II randomized open-label	17–40	34 (Lymphoma)	1. Goserelin 3.6 mg s.c. 28 ± 3 days + standard chemotherapy 2. Standard chemotherapy alone	FSH and E2 levels at 6 months; overall response rate in lymphoma patients** at 6 months; GnRH-related AEs	6 months
NCT03475758	Goserelin for Ovarian Protection in Premenopausal Patients Receiving Cyclophosphamide, Sponsor Assiut University	Phase II randomized open-label	NR (Child and adult)	100 (Cancer patients)	1. Goserelin 3.6 mg s.c. every 4 weeks + cyclophosphamide containing chemotherapy 2. Cyclophosphamide containing chemotherapy alone	Rate of ovarian failure at 1 year (assessed by hormonal profile – FSH, LH, estradiol – every 6 months)	1 year

*'Cyclophosphamide 6 g/m2, Ifosfamide 50 g/m2, Procarbazine 4 g/m2, Lomustine 350 mg/m2 or Melphalan 140 mg/m2 or a combination of these drugs; ** determined by tumor assessments from radiological tests (CT scan, MRI, Positron-emission tomography or physical examinations); AFC, Antral follicular count; AMH, Anti-Mullerian hormone; BMD, Bone Mass Density; FSH, Follicle-stimulating hormone; NR, not reported.*

NIH Trials Adolescent and Pediatric population

Blumenfeld et al, 2019

This review summarizes the pros and cons of GnRHa co-treatment for fertility preservation, suggesting 5 theoretical mechanisms for GnRHa action:

(1) simulating the prepubertal hypogonadotropic milieu
(2)direct effect on GnRH receptors
(3) decreased ovarian perfusion
(4) upregulation of an ovarian-protecting molecule such as sphingosine-1-phosphate
(5) protecting a possible germinative stem cell.

Clin Med Insite Reprod Health

OVARIAN TRANSPOSITION

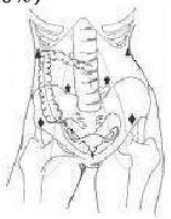
(The ovarian dose is reduced by transposition to 5–10%)

A) Medial transposition

Behind the uterus.

B) Lateral transposition

up to the pelvic sidewall at least 3cm from the upper border of the radiation field.



techniques * by laparotomy during surgery.

* by laparoscopy

- higher doses of radiation are more likely associated with vascular damage of transposed ovaries.

Ovarian Transposition

Cost of FP

- Sperm banking – 800
- Egg or embryo freezing – 8000 to 10,000
- Ovarian tissue freezing – surgical package, trying to bundle with ports or bone marrow procedures – in process of solidifying this plan
- Lupron – 500 per month

Practical Considerations

- Time involved- MUST BE COMPLETED PRIOR TO INITIATING ANY TYPE OF THERAPY
- Consult within 48 hours, Prefer in clinic at Reproductive Medicine at Springhill
- Can offer inpatient consults within 24 hours (Monday-Friday
- We offer phone consults
- Some funding available for consults (donation from Climb For Cancer)/medications

Pregnancy and Children After Treatment

- Males should wait 1- 2 years after treatment and females 6 mos before trying to conceive
- Damage to sperm and eggs from treatment may occur, but appears to repair in 6 mos to 2 years
- Birth defect rates of children born to cancer survivors are similar to that of the general public ~2-3%
- No unusual cancer risk has been identified in the offspring of cancer survivors, except in genetic cancer syndromes

CANCER AND PRESERVING YOUR FERTILITY:
UF Health HOPE Network

Helping Oncofertility Patients become Educated


UF Continuing Medical Education
UNIVERSITY of FLORIDA
UF HEALTH
ONCOFERTILITY AND FERTILITY PRESERVATION SYMPOSIUM 2022
Current Considerations and Options
March 19, 2022 | 8:00am - 4:30pm
Harrell Medical Education Building | Gainesville, FL
Designed to cover the current and updated guidelines in male and female cancer survivors, and the most current strategies for non-oncologic fertility preservation.
Hear recent case studies in Oncofertility.
Learn current strategies for fertility preservation in cancer survivors.
Learn how to discuss options to help survivors build a family after treatment.
FertilityPreservation.cme.ufl.edu
In-Person and Virtual options available!
This symposium has been endorsed by FLASCO:
The Florida Society of Clinical Oncology
Funded by Climb For Cancer Foundation

Questions…