

Fertility & Family Building for Survivors (female)

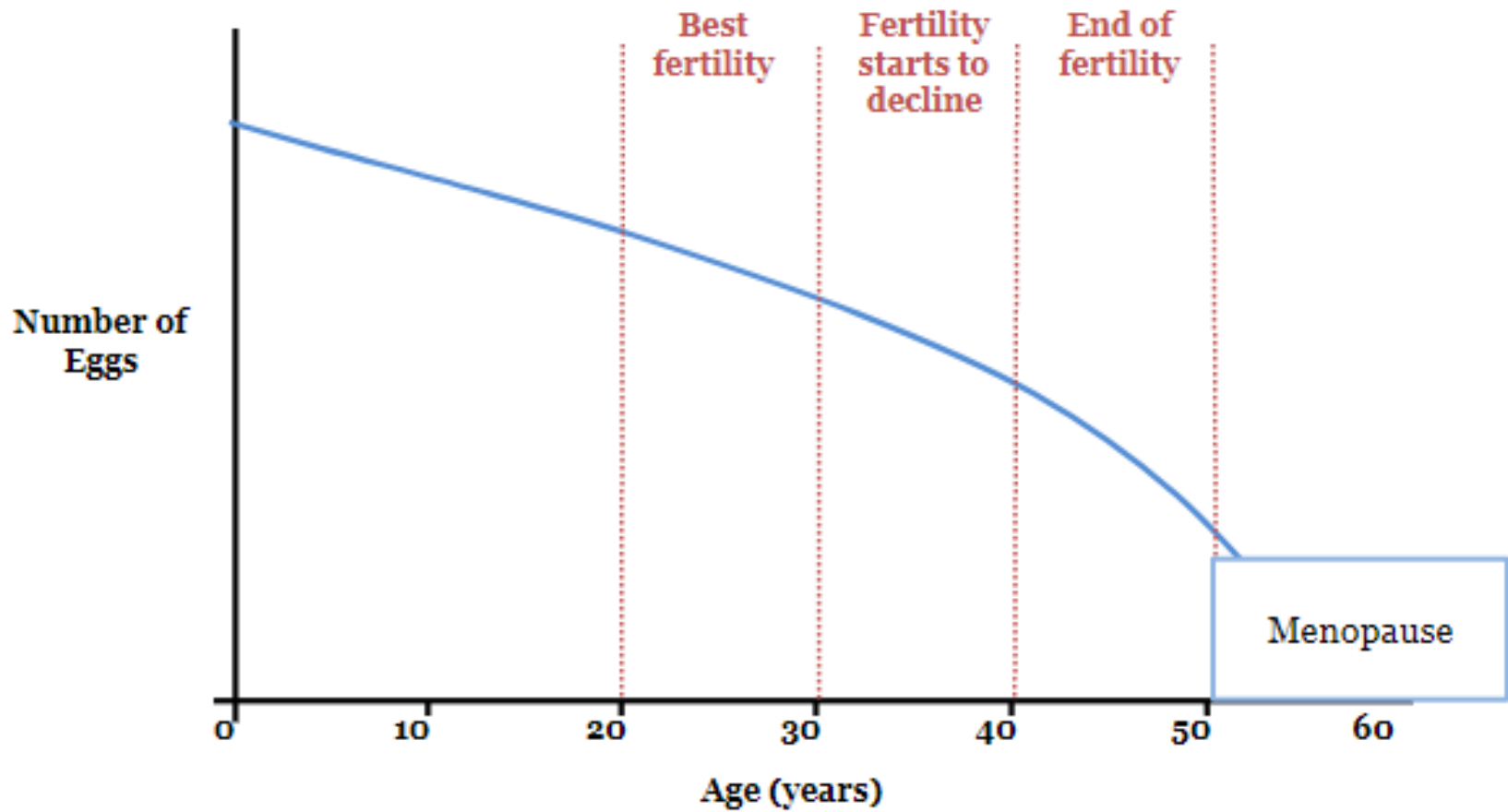
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Ovarian Reserve



Magnitude of fertility risk after cancer treatment depends on:

- Drug class and cumulative dose
- Radiation field, number of treatments, and cumulative dose
- Extent of surgical therapy
- Age
- Genetic factors

Childhood Cancer Survivor Study (CCCS)

- The largest database on risk of infertility in cancer survivors.
- Cohort study of several thousand five-year cancer survivors from 26 U.S. and Canadian institutions who were < 21 years at time of diagnosis and who had an eligible malignancy: leukemia, central nervous system (CNS) cancer, Hodgkin lymphoma, non-Hodgkin lymphoma, Wilms' tumor, neuroblastoma, soft-tissue sarcoma, or bone tumors.
- Pregnancy rates among female survivors was lower than in female siblings (RR 0.81, 95% CI 0.73-0.90).
- More than 10-fold increased risk of premature menopause.
- Poor prognostic factors included:
 - Hypothalamic/pituitary radiation dose ≥ 22 to 30 Gy.
 - Ovarian/uterine radiation dose >5 Gy.
 - A summed alkylating agent dose (AAD) score of three or four.
 - Treatment with cyclophosphamide or lomustine.

Cyclophosphamide Equivalent Dose (CED) Rate Ratios for Premature Menopause

- Alkylating agents are widely used for the treatment of cancers of children and adolescents and are associated with infertility, ovarian failure, and premature menopause

Variable	CED			AAD		
	RR	95% CI	p-value	RR	95% CI	p-value
Age	1.14	1.09 to 1.20	< 0.001	1.13	1.07 to 1.19	< 0.001
Minimum ovarian dose						
Other cancers						
None	1.00			1.00		
1 to 99 cGy	2.96	0.92 to 9.50	0.069	4.25	1.18 to 15.26	0.027
≥ 100 cGy	11.68	3.59 to 38.04	< 0.001	16.77	4.55 to 61.88	< 0.001
Hodgkin lymphoma						
None	13.86	4.04 to 47.57	< 0.001	9.88	1.65 to 59.24	0.012
1 to 99 cGy	10.04	3.40 to 29.65	< 0.001	12.73	3.55 to 45.57	< 0.001
≥ 100 cGy	10.76	3.32 to 34.91	< 0.001	10.73	2.70 to 42.64	< 0.001
CED (mg/m²)						
0	1.00					
> 0 to < 4,000	0.56	0.07 to 4.27	0.578			
≥ 4,000 to < 8,000	2.74	1.13 to 6.61	0.025			
≥ 8,000	4.19	2.18 to 8.08	< 0.001			

Options for people with ovaries

	Before Treatment	During Treatment	After Treatment	Status
Egg Freezing	X		X	Standard
Embryo Freezing	X		X	Standard
Ovarian Tissue Freezing	X		X	Standard*
In Vitro Maturation	X		X	Experimental
Ovarian Transposition	X			Standard
Conservative Surgery		X		Standard
GnRHa		X		Experimental
Natural Conception			X	Standard
In Vitro Fertilization			X	Standard
Donor eggs or embryos			X	Standard
Adoption			X	Standard
Gestational Surrogacy			X	Standard

Before (or After) Treatment Egg and/or Embryo Freezing Post-Puberty



- Embryo freezing has been used routinely for storing surplus embryos after IVF for many years
- Egg freezing is now preferred for those who do not have a committed lifetime male (AMAB) partner
 - Avoid use of donor sperm
 - Fewer religious or ethical concerns
 - Lower up-front cost per cycle
 - Less information about future reproductive potential



Egg Freezing (Oocyte Vitrification)

- **1999**
First human pregnancy
- **2002-2007**
Studies showed good survival, fertilization, cleavage rates
- **2006-present**
Studies showed pregnancy rates similar to that of fresh IVF
- **October 2012**
ASRM deemed egg freezing no longer experimental



120 microns

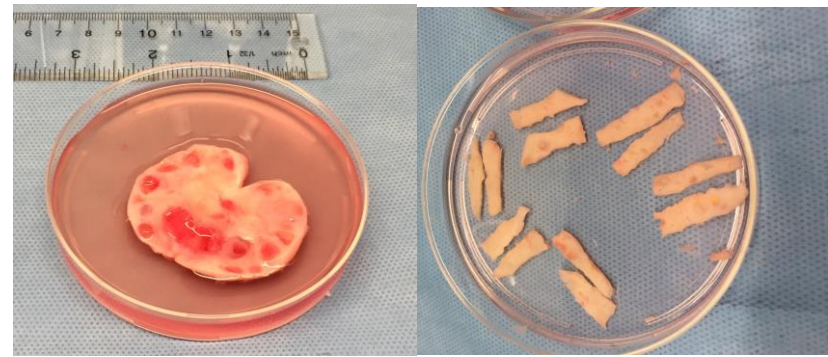
Metaphase II
(mature oocyte)

Before (or After) Treatment Egg and/or Embryo Freezing



- Ovarian stimulation and retrieval takes about 2 weeks total
- Involves injectable stimulation medications each evening
- No longer cycle-dependent, could begin at any time
- Egg retrieval procedure is done under a light anesthesia, takes about 20 minutes, and there are no incisions, sutures, or scars
- For hormonally-sensitive tumors (e.g. breast cancer), goal is to minimize estrogen exposure during ovarian stimulation, add letrozole or tamoxifen.

Ovarian Tissue Freezing Pre-Puberty



- In 2019 ASRM deemed ovarian tissue cryopreservation (OTC) no longer experimental.
- Only considered if a patient is not a candidate for egg or embryo freezing (i.e. pre-pubertal) as the most mature technology is always recommended.
- Can be performed immediately.
- Requires surgery.
- What to do with the tissue in the future?
 - Ovarian Tissue Transplantation (OTT)
 - Orthotopic or heterotopic
 - >185 livebirths reported worldwide
 - Or possibly in vitro follicle maturation? - IFM
 - 3-D scaffold system
 - No livebirths yet

Before Treatment Ovarian Transposition

Protect the ovaries from radiation by surgically moving the ovaries up out of the pelvis (requires laparoscopy)

Because of radiation scatter, the ovaries are not always protected and this technique is not always successful

During Treatment Ovarian Shielding

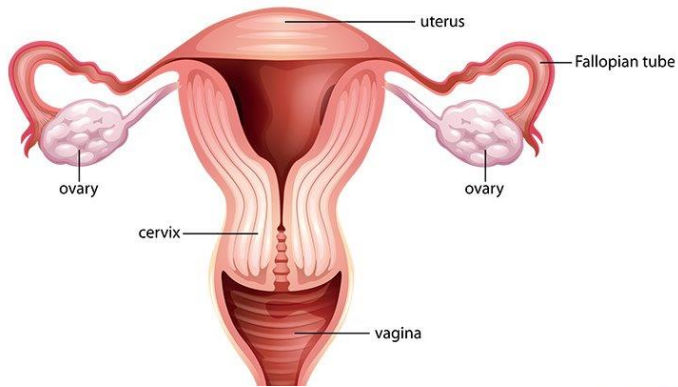
Protect the ovaries from radiation by shielding



During Treatment Conservative Surgery

Trend toward less aggressive surgery in young patients with cancer

- Can the uterus be preserved?
- Can the cervix be preserved?
- Can one ovary be preserved?
- Can cystectomy be performed instead of oophorectomy?



During Treatment

GnRH Analog Co-treatment

- Ovarian suppression during chemotherapy
- e.g. leuprolide acetate, or leuprorelin, goserelin, buserelin
- Almost 1,000 publications in the literature, but few good studies
- GnRHa may be offered in hopes of reducing the likelihood of chemotherapy-induced ovarian insufficiency. However, GnRHa should not be used in place of proven fertility preservation methods.

After Treatment

- **Do you have frozen eggs or embryos?**
- **Do you have frozen ovarian tissue?**
- **What is your current ovarian reserve?**

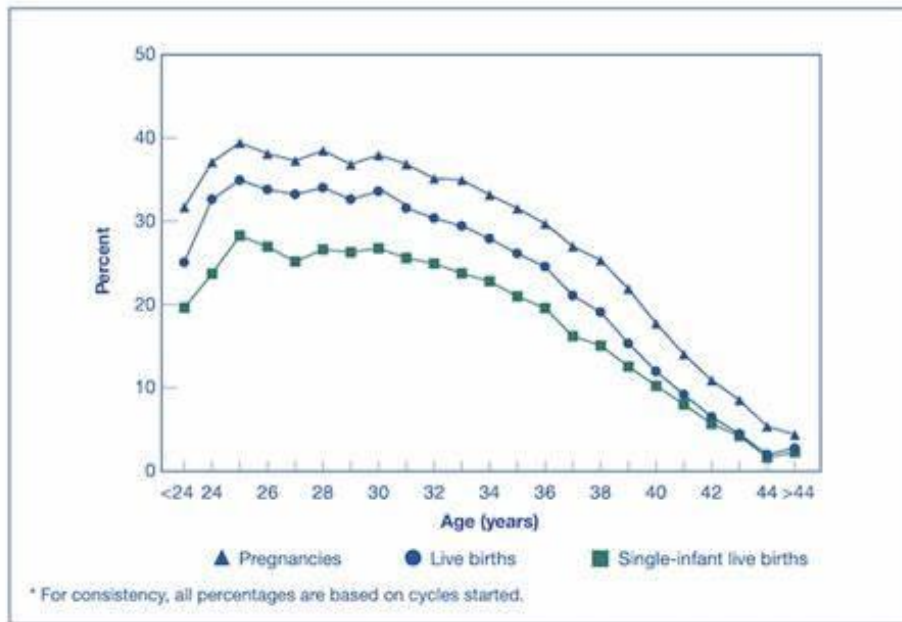
*** Fertility Assessment**

- Blood draw for anti-mullerian hormone (AMH)
- Blood draw for FSH, E2 (if menses, cycle days 2, 3, or 4)
- Ultrasound for antral follicle count (AFC)
- Growing eggs and sperm may be damaged by chemotherapy and radiation, but there may be a partial repair process during the first 6 to 24 months after treatment
- Whether infertility is transient or permanent, and the duration of transient infertility, cannot be predicted reliably.

After Treatment Menstruation ≠ Fertility

Figure 15

Percentages of ART Cycles Using Fresh Embryos from Fresh Nondonor Eggs That Resulted in Pregnancies, Live Births, and Single-Infant Live Births, by Age of Woman,* 2016



Average age of menopause ~51

Average age of last birth ~41

In the natural reproductive lifespan there is expected to be about *one decade* of regular menstrual periods without fertility

Periods are neither necessary nor sufficient for family building

Amenorrhea is an extremely late finding

If you are sexually active and do not wish to conceive, you must use birth control

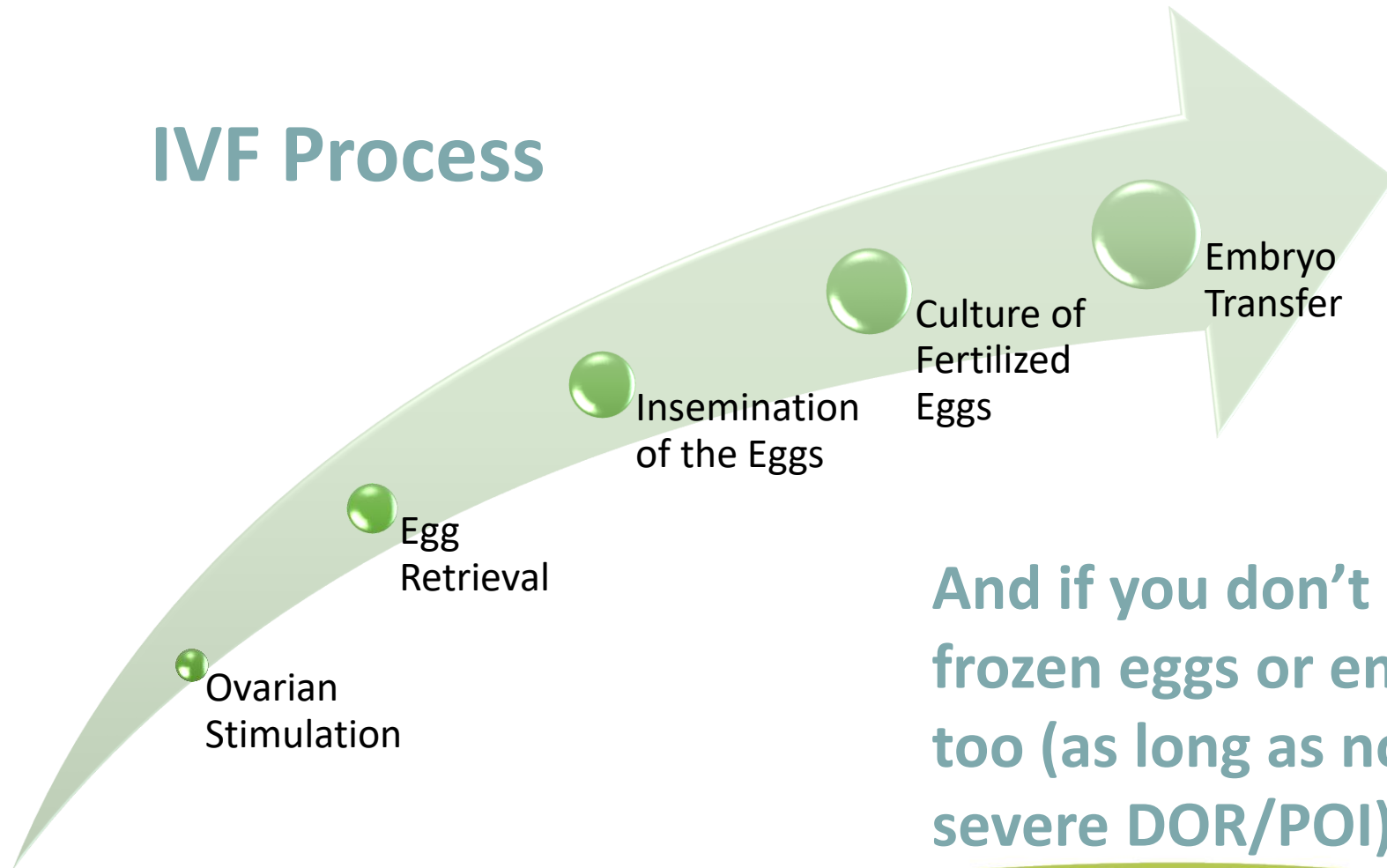


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If you have frozen eggs or embryos: Assisted Reproductive Technology (ART)

IVF Process



**And if you don't have
frozen eggs or embryos
too (as long as no
severe DOR/POI)**

If you have frozen ovarian tissue: Consider Ovarian Tissue Transplantation (OTT)

- Experimental, would need to find the right surgeon.
- Transplantation of your own tissue may not be used if you have a type of cancer in which your tissue might “re-seed” your cancer in the future, such as ovarian cancer or some types of leukemia or lymphoma.
- OTT is the only fertility preservation method that holds promise in restoring endocrine function (i.e. relief from menopausal symptoms), not just fertility.

If you have no frozen material and you have premature menopause

- Natural conception?
 - 5-10% lifetime chance
- Many other good forms of family building
 - IVF with donor egg
 - Donor embryo
 - Adoption

• If your pituitary gland has been severely affected by radiation treatment

- Overcome with gonadotropin injectable medication as utilized in IVF

• If your uterus has been severely affected by radiation treatment

- Increased risks of preterm birth, fetal growth restriction, and stillbirth
- Gestational carrier/surrogacy

Fertility and Survivorship



- **No increased risk** of birth defect rates in children of cancer survivors (similar to general population, ~3%).
- **No increased risk** of chromosomal abnormalities (e.g. Down syndrome, Turner syndrome) in children of cancer survivors.
- **No increased risk** of cancer in children of cancer survivors – unless the tumor is a component of an inherited cancer syndrome, such as retinoblastoma or Li-Fraumeni, in which case testing of embryos (preimplantation genetic testing for a monogenic condition = PGTm) can be performed for prevention.
- Survivors of ovarian or breast cancer who are positive for BRCA1 or 2 mutation have a 50 percent chance of passing the mutation to their children, unless they utilize PGTm for prevention.
- Pregnancy after cancer does not appear to trigger recurrence, even after breast cancer.

Questions

