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NYSCHP September CE Webinar

Fertility Preservation Options for Oncology Patients

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Learning Objectives

- To provide fertility preservation options and modalities
- To review the NYS mandate on coverage for medical fertility preservation and medications
- To discuss antineoplastic therapy degree of fertility risks and fertility preservation

Disclosure

- The presenter have nothing to disclose

Cancer Cases

- Annual worldwide new cancer cases are projected to increase by more than 50% in the next two decades (14 - 21 million from 2012 through 2030)
- Overall cancer death rates continue to decline, with a 13% drop in the United States from 2004 through 2013 (www.cancer.gov)
- Number of cancer survivors continues to increase and has reached nearly 14.5 million in 2014 in the United States, where it is expected to rise to 19 million by 2024
- About 9% of new cancer cases are diagnosed during the reproductive age, and, as of January 2016, there are 8 million female cancer survivors in the United States, of which 5% are 15-40 years of age

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Cancers in Reproductive Aged Females

- Lymphoma
- Leukemia
- Breast Cancers
- Sarcomas
- Pelvic cancers PLUS>>>

- Treatments with chemotherapy (especially alkylating agents) and pelvic radiation can cause sterilization, hormone receptor adjuvants, surgery, bone marrow transplants

- Age has direct relationship with diminishing ovarian reserve

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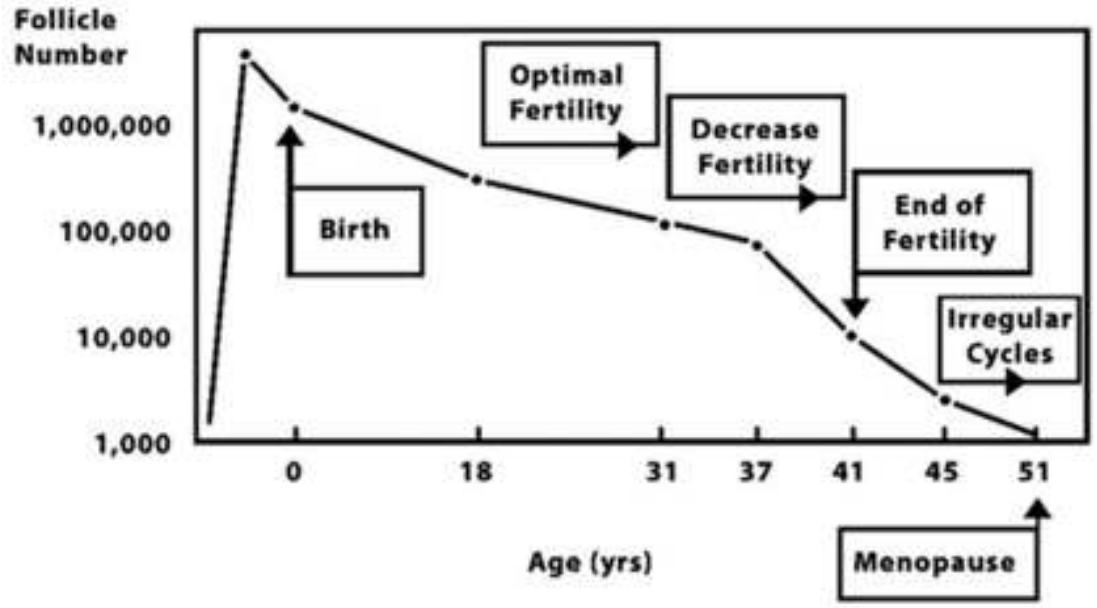
Number of Oocytes in Females



The decreasing follicle pool and age related decline in female fertility

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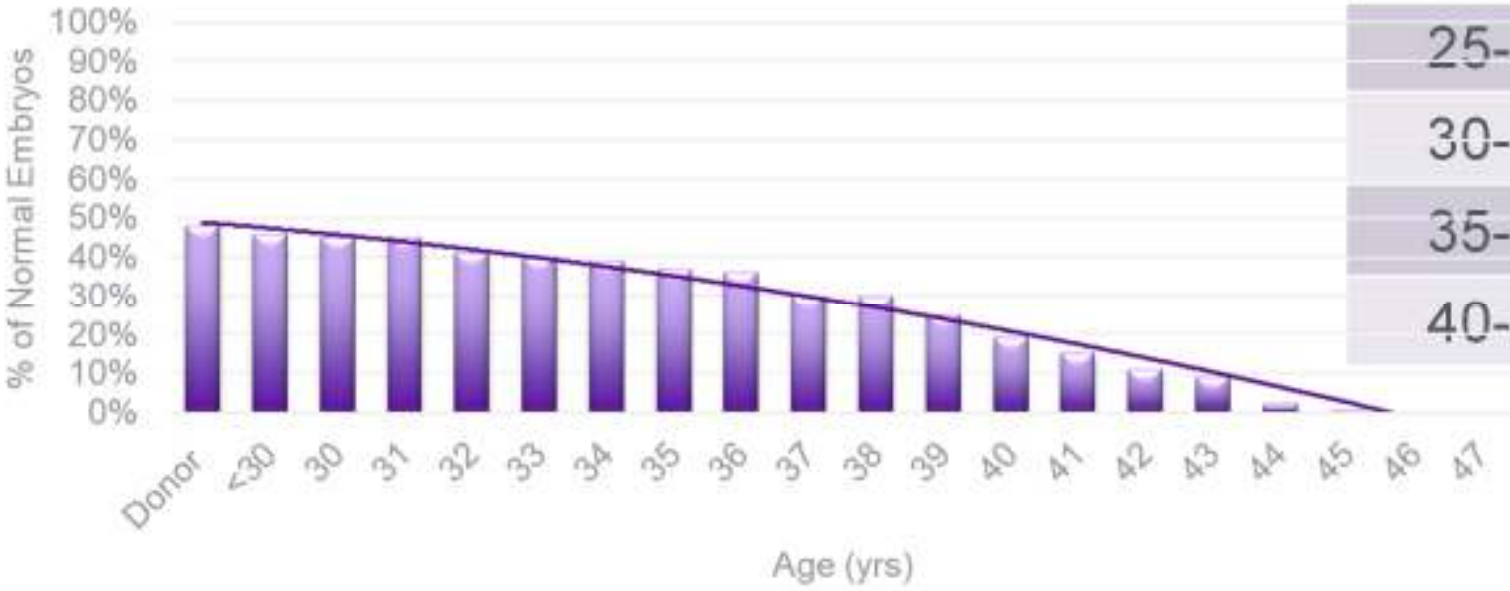
Age and Pregnancy Rates/Euploid Embryos



Age (years)	Lower pregnancy rates by
25-29	4-8%
30-34	15-19%
35-39	26-46%
40-45	95%

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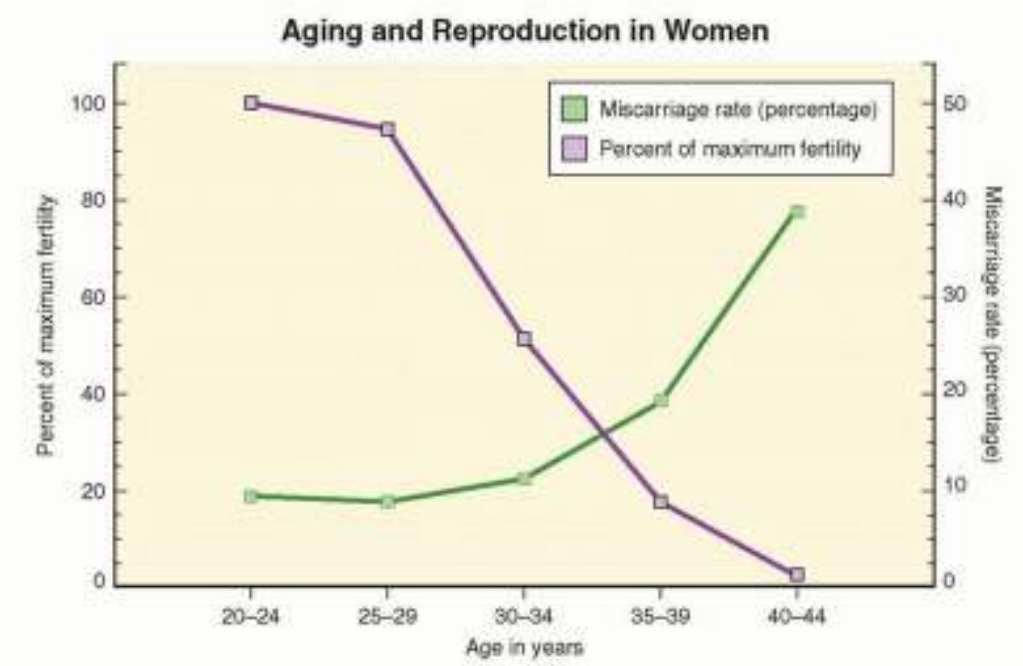
Fertility Decline with Advanced Age

- US average age at first pregnant increase from 22.5 in 1970 to 26.3 in 2014
- In US 2014
  - 21.1% mom had first birth at age of 30-34 years
  - 9.1% at age of 35 or later
  - 10x delay from 1970



Importance of early fertility preservation

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Reasons to Preserve Fertility at a Younger Age

- Pregnancy rates are higher in younger than older women
- Miscarriage rates are lower in younger than older women
- Delays in childbearing

Female Fertility Preservation Options

Reproductive Aged Females

- Freezing embryos (eggs fertilized with sperm)
- Mature oocyte cryopreservation
- Freezing ovarian tissue (experimental)
- Ovarian transposition (cervical cancer)
- GnRHa prior to chemotherapy (breast cancer? Hematologic cancers?)

Prepubesence Aged Females

- Freezing ovarian tissue (experimental)
  - Only option

Valsamakis et al Int J Mol Sci Int J Mol Sci 2022 Feb 18;23(4):2287. doi: 10.3390/ijms2304228

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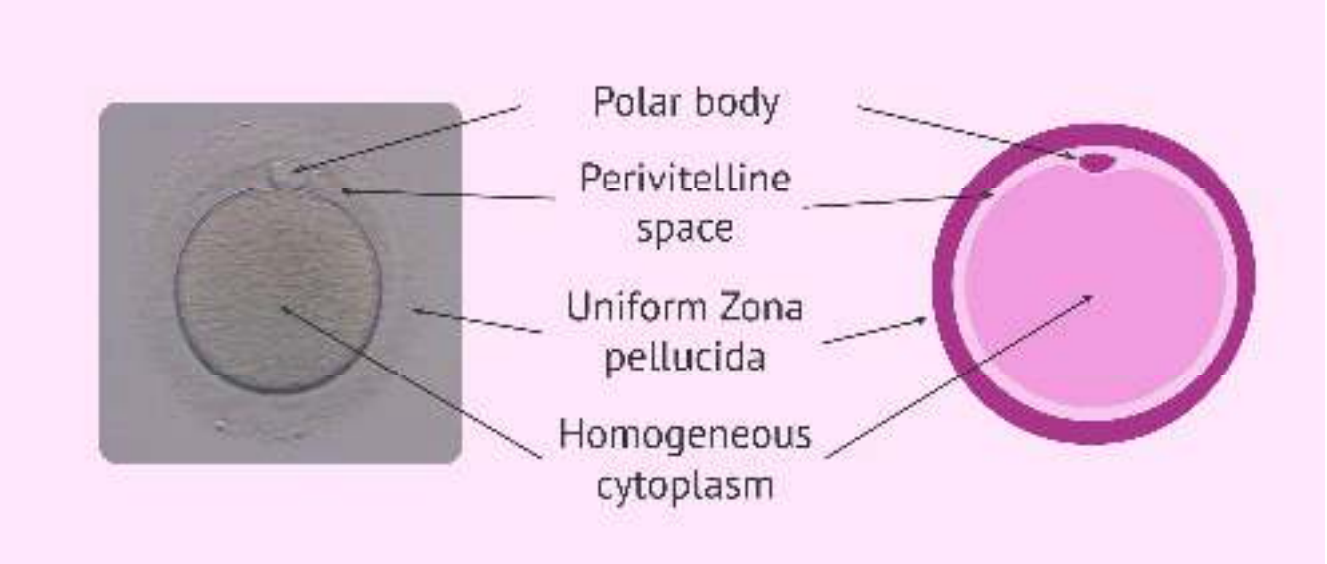
Freezing Oocytes

- First live birth in 1986 by Chen
- 12 years ago vitrification allow for improved survival from thaw
- Zona pellucida after freezing hardens, ICSI (intracytoplasmic sperm injection) required to allow for comparable fertilization
- Frozen eggs from females 35 years or younger results in 65% cumulative live birth
- Prepubertal girls cannot freeze oocytes and can opt for experimental ovarian tissue cryopreservation



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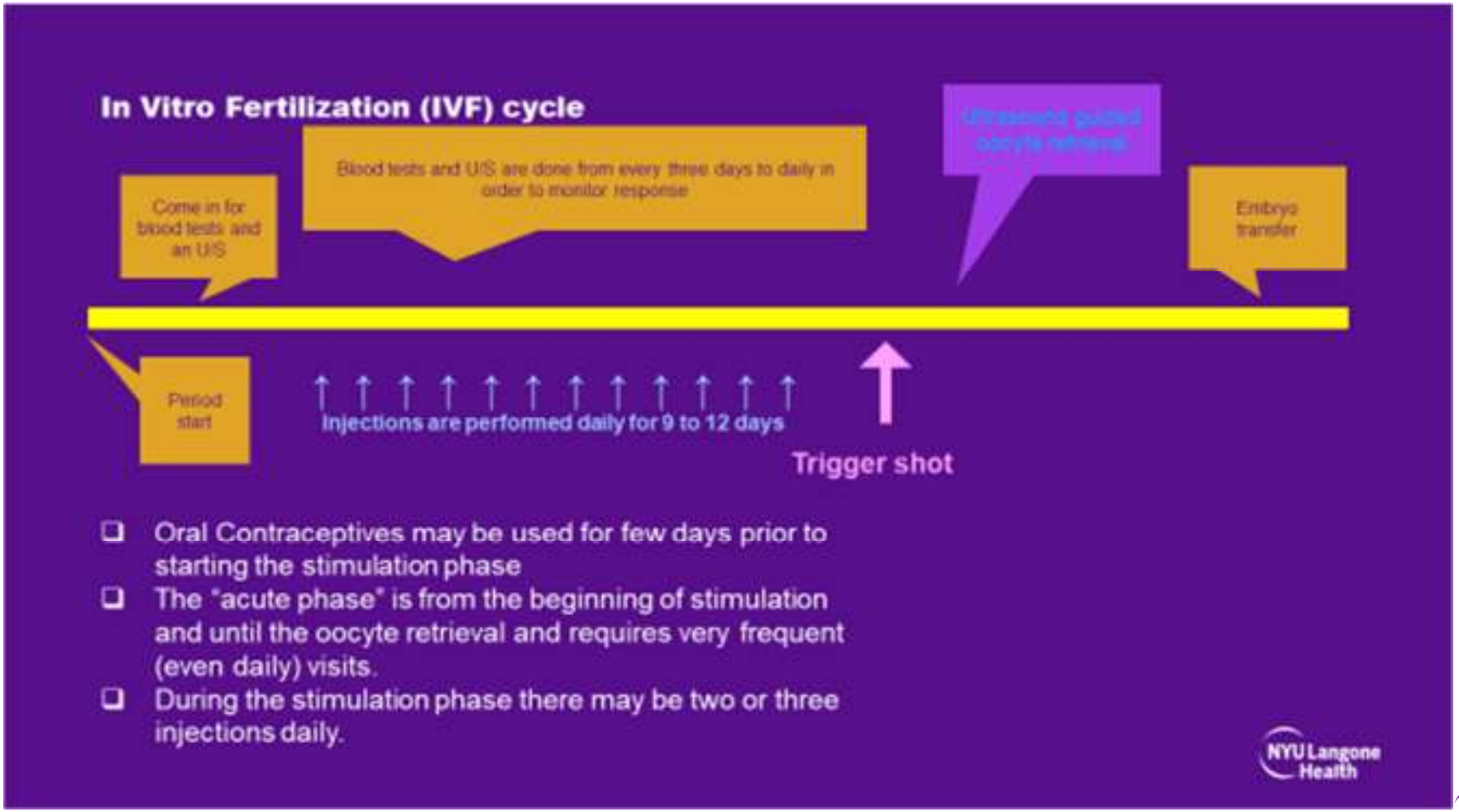

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Ultrasound Guided Egg Retrieval

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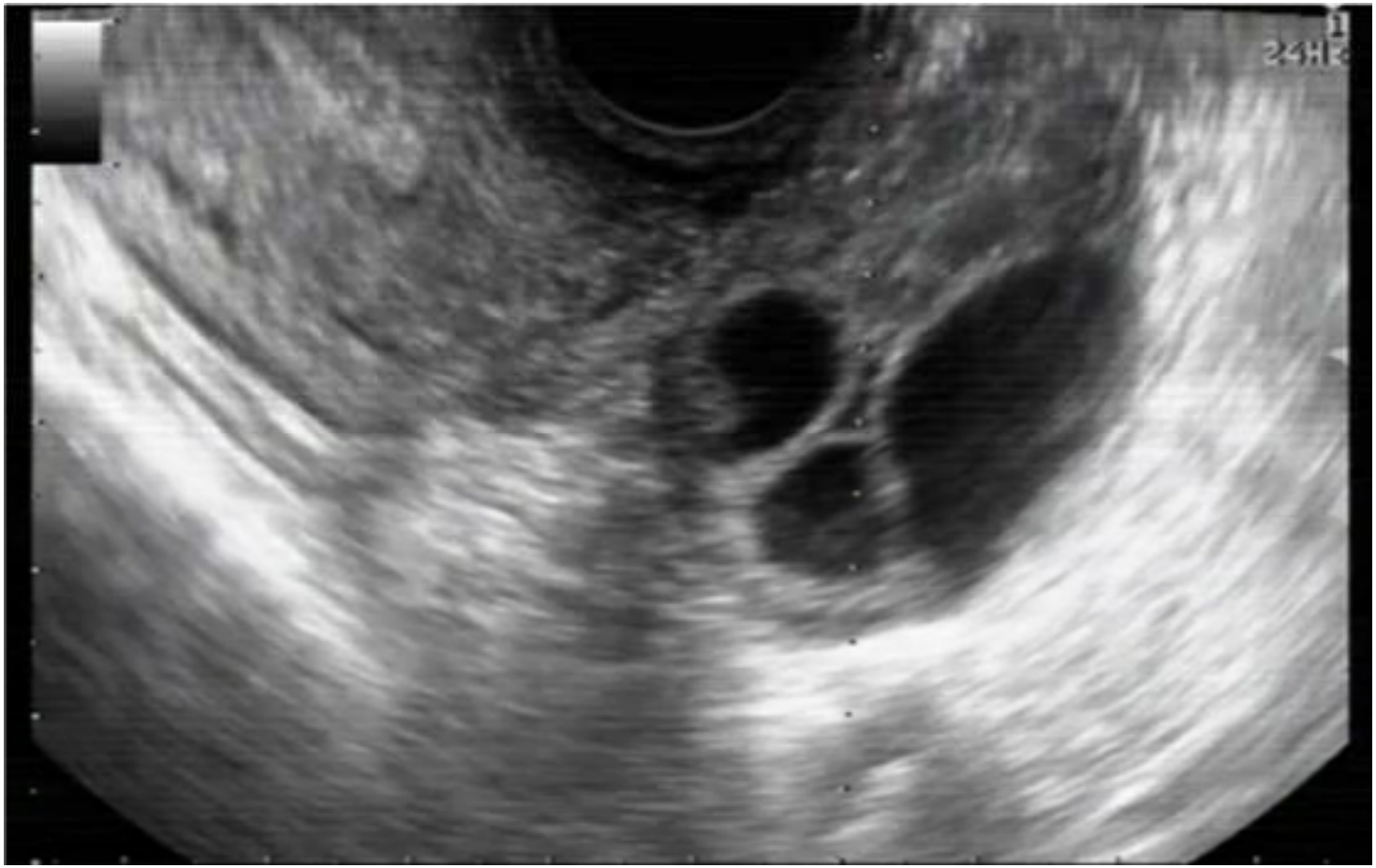
Oocyte Retrieval



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After the Oocyte Retrieval (egg and embryo freeze)

- Symptomatic
- Fluid in abdomen (fluid shift due to third spacing of fluids from hormonal stimulation and oocyte production by ovaries)
- Enlarged ovaries
- Cysts in ovaries
- Positive HCG

- Can give depo-Lupron (provided not affect overall outcomes)
- May need a week to recover from ovarian hyperstimulation syndrome (OHSS)
- Balancing when to start chemo vs OHSS

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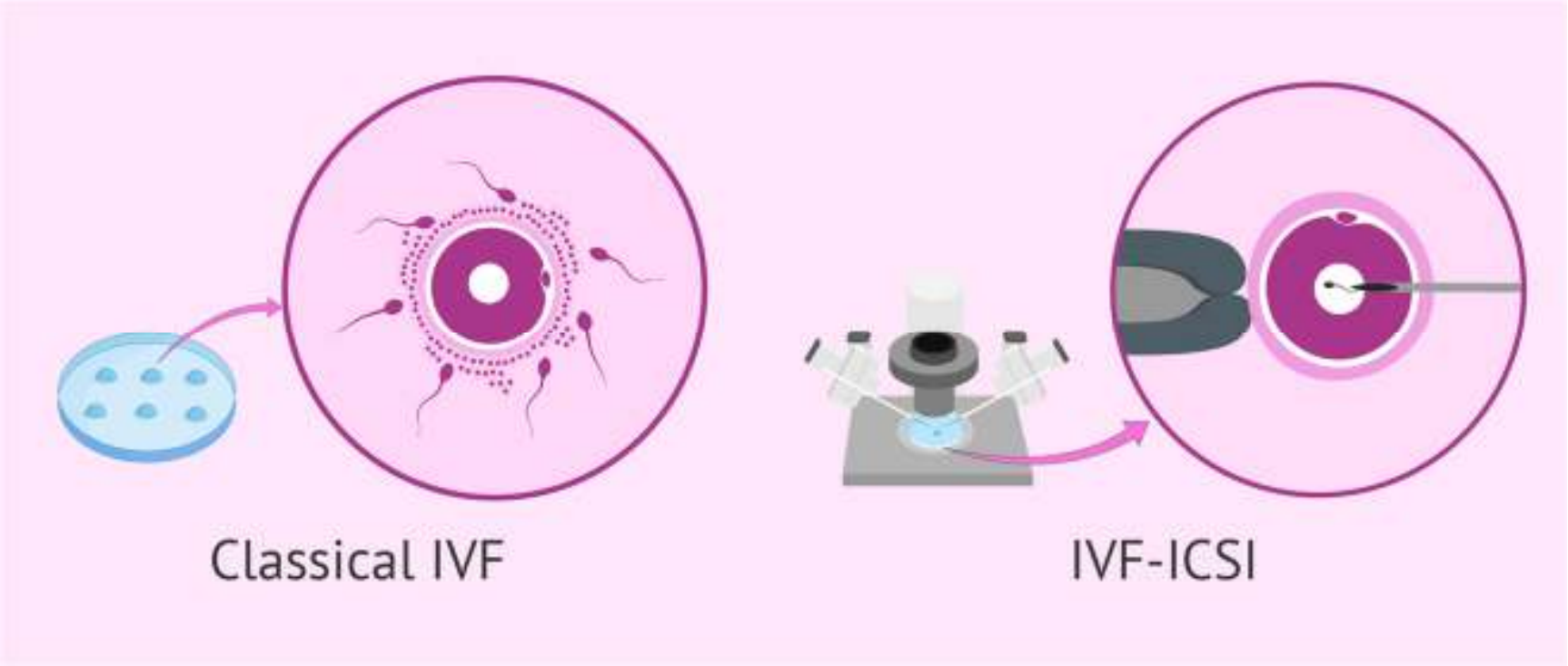
Freezing Embryos

- Established 5 years after first IVF birth (about 40 years ago)
- Vitrification (prior slow freeze) results is comparable if not higher pregnancies to fresh embryo transfers
- Must have designated sperm source (male partner, donor sperm, known male donor)
- Human oocyte one of the largest cells and large amount of cytoplasm. Slow freeze would cause ice crystal and damage meiotic spindle and other intracellular organelles.

Fertilizing the Eggs with Sperm



https://www.youtube.com/watch?v=GTiKFCkPaUE

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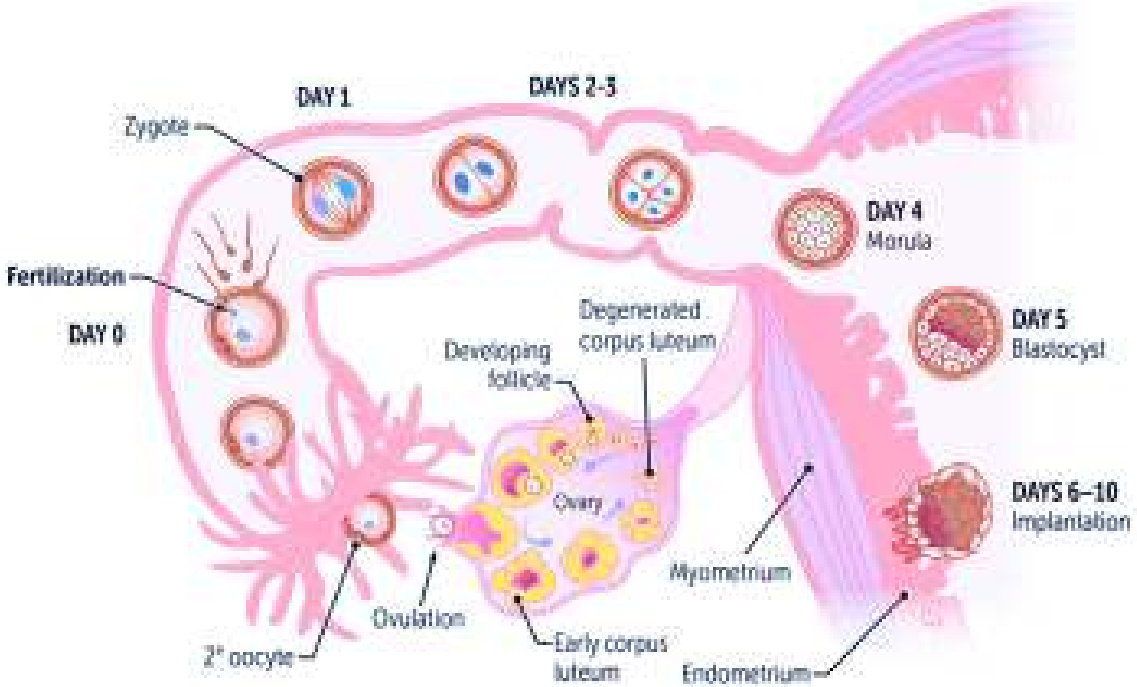

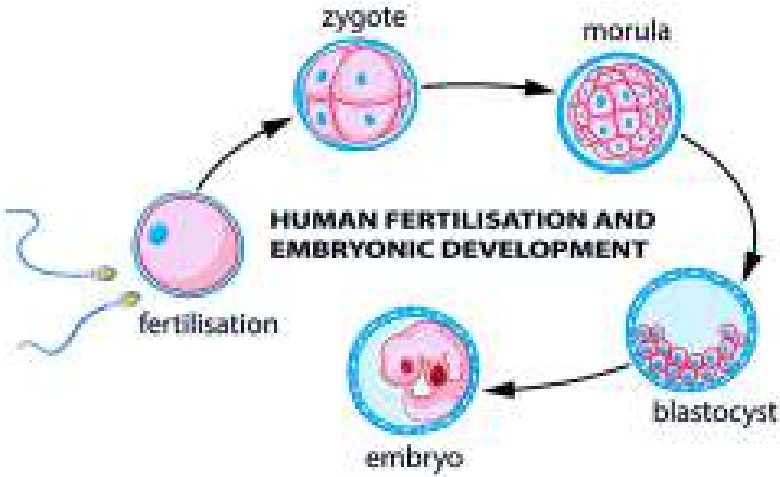

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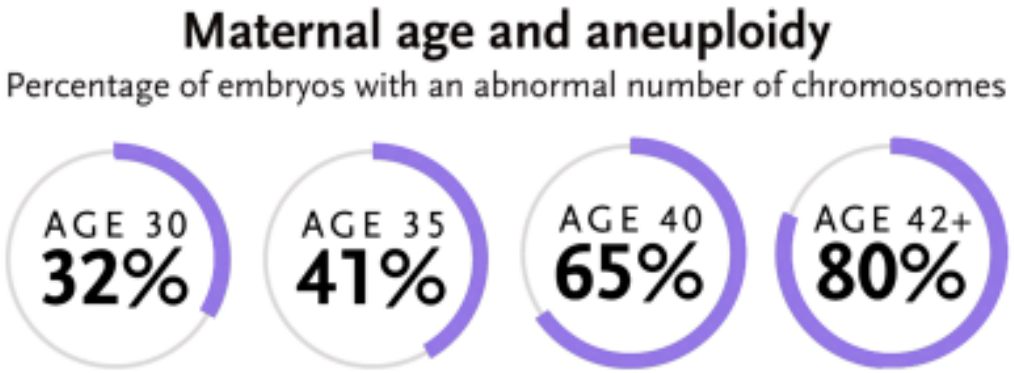
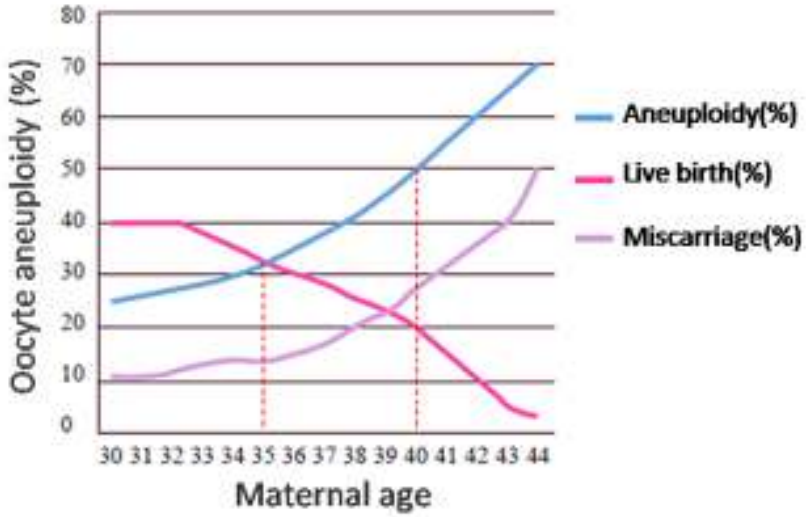
Embryonic Aneuploidy and Maternal Age





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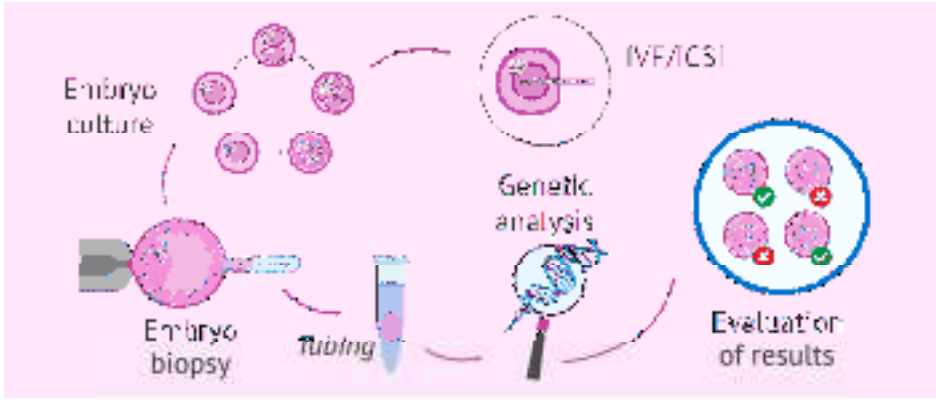
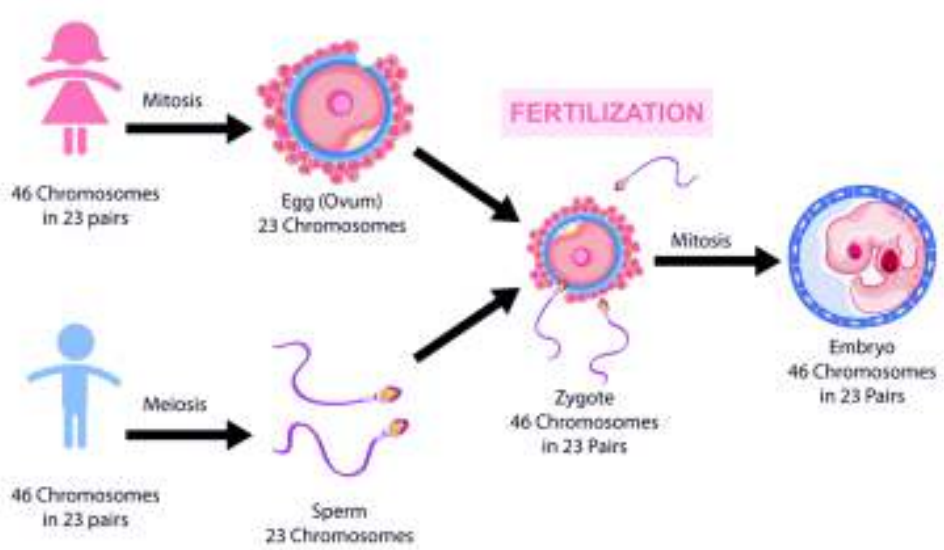
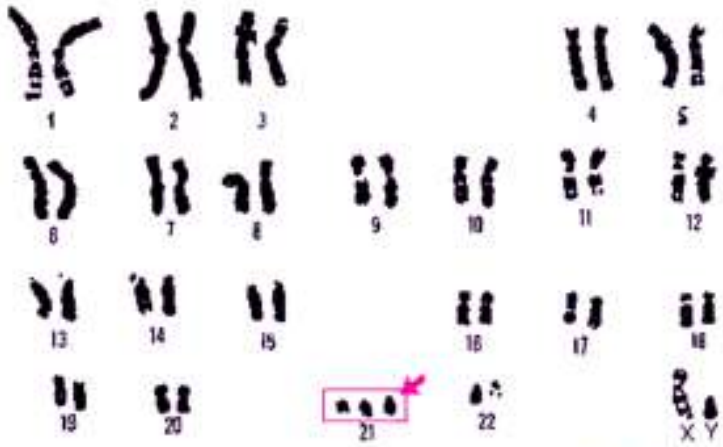
Pre-implantation Genetic Testing

- Aneuploidy (normal: 46 chromosomes: 23 from egg and 23 from sperm)
- 90-95% accurate, Not covered by insurance







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Frozen Eggs (when returning after treatment and in remission)

- ICSI
- Grow to day 5 (blastocyst stage)
- Preimplantation Genetic Embryo Testing
  - PGT-A (aneuploidies) — most insurances do not cover this
  - PGT-M (monogenic disorders) — some insurances cover this
  - HLA
  - Structural rearrangements
- Embryo Transfer
  - Fresh embryo transfer on day 5 or if **frozen embryo**, thaw embryo and transfer
  - or refreeze/await PGT results, then Frozen embryo transfer

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Hereditary Cancers

- Preimplantation genetic testing monoclonal
- BRCA mutations – Need to develop assays to test the trophectoderm cells
  - Takes 2-4 months, if freezing embryos, may not be able to test embryos
- If freezing oocytes, can thaw eggs, perform ICSI and grow to blastocysts, PGT-M
- Takes time to make assay to be able to test embryos for genetic mutation
- Need to test embryos fresh (not frozen) for genetic

Factors in Considering Cryopreservation

1. Age: The younger the woman is at the time of oocyte retrieval and egg/embryo freezing, the higher the live birth rate.
2. Delay in cancer treatment: Oocyte and embryo cryopreservation require controlled ovarian hyperstimulation, delaying the administration of chemotherapy by a minimum of 10-12 days. Confirmation with oncologists/surgeons needed prior to starting stimulation. Random-start approaches to ovarian hyperstimulation are equally effective, and such delays are not necessary.
3. Hormone sensitivity of malignancies: If ER + breast cancer, controlled ovarian hyperstimulation with agents that block estrogen production given in conjugation with gonadotropins result in low peak estradiol levels. Stimulate with an aromatase inhibitor along with daily follicle-stimulating hormone (FSH). Aromatase inhibitor is continued until the day of ovulation trigger and even later. Leuprolide acetate along with human chorionic gonadotropin given to trigger oocyte meiosis. Can still give depo Lupron after egg retrieval. Will have positive pregnancy tests if HCG given

Ovarian Tissue Cryopreservation and Transplantation

- Animal studies for more than 60 years.
- First human ovarian transplantation with cryopreserved ovarian tissue was performed in 1999 by Kutluk Oktay.
- In 2004, the first live human birth from frozen ovarian tissue was reported.
- Studies in pre- and postpubertal women indicate that autotransplantation of frozen-thawed ovarian tissue is useful for the restoration of endocrine function before and after puberty. Furthermore, ovarian endocrine activity can be restored in more than 95% of cases.[1]
- Still considered experimental
- Literature reporting live births has been case reports.
- To date, at least 130 live births have been reported globally following the transplantation of cryopreserved ovarian tissue with pregnancies achieved in 1/4 to 1/3 of cases.

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Freezing Ovarian Cortical Tissue

- Instant menopause
- Experimental
- Can reseed
- Prepuberty
- Ovarian cortex
- Historic slow freeze, now more vitrification
- Orthotopic (remaining ovary/ovarian fossa/broad ligament) vs.
- Heterotopic transplantation (forearm, abdomen subcutaneous, anterior abdominal wall, beneath peritoneum, or in rectus muscle)
- Biggest factor for failure: Revascularization (ischemia)

Cryopreservation for sperm

- Freeze semen (from ejaculate in males from puberty to adulthood)
  - Can thaw sperm for IUI (intrauterine insemination) and IVF (in vitro fertilization)/ICSI (intracytoplasmic injection)
- Freeze sperm extracted (from testes in prepuberty males and adult males with outflow tract obstruction)
  - Requires anesthesia in children or anesthesia/local anesthetic in adult males
  - can only use in IVF with ICSI

ADV/DISADV	Embryo	Oocyte	Ovarian Tissue
Sperm is required	+	–	–
Shared ownership	+	–	–
Delays chemotherapy	+	+	–
Can be used in prepuberty	–	–	+
Requires stimulation	+	+	–
Considered experimental	–	–	+
Live births reported	+	+	+
Resume endocrine fx poss	–	–	+[a]
Requires surgery	–	–	+
Risk of reseeding cancer	–	–	+

What do the Fertility Specialists Need to Know before starting Fertility Preservation Cycles?

- Female's Age
- Desire for having children in their future
- Partner Status [single or spouse (male/female)]
- Presence of Cancer on Ovaries/Peritoneum (risk of recurrence)
- Health of Patient (unstable)
- Anesthesia Risks (airway, sleep apnea, BMI, etc) – outpatient facility
- Accessibility to Ovaries using TVS
- Timeline of Delay in Treatments to Allow for Oocyte preservation/IVF egg retrieval
- Type of Cancer (if cancer is sensitive to hormones?)
- Hereditary Cancer or potential to be hereditary cancer

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Counselling Patients with Newly Diagnosed Cancer on Fertility Preservation

- Involves discussion patient and if applicable significant other/legal parent/guardian(s)
- Access to care
- Ability to afford costs (fertility preservation, cancer care, parking, traveling to doctor's and imaging appointments, etc)
- Juggling multiple appointments (with possibly the surgeon, oncologist, fertility specialists, pediatrician, 2nd opinions) and trying to not lose their jobs
- Stages of Grief (Shock, Denial, Anger, Bargaining, Depression, Acceptance and Hope)

Life After Cancer: Hope of Having Children Coming back for the Frozen Eggs/Embryos/Sperm

- Consult Reproductive Endocrinologist/Infertility Specialists
  - Questions about freezing eggs/sperm/embryos
  - Team effort with oncologist (when to start to have children)
  - Fertility at 40 vs 30 --- Difference with fresh vs. frozen transfer
  - Counselling on the effects of oncology treatments on fertility/pregnancy (Joint counselling from oncologist/MFM/REI)
  - Checking effects of treatments (ovarian reserve testing)

Other Options if Not Autologous Oocytes/Sperm

- Donor eggs or sperm
- Donor embryos
- Gestational surrogate
- Adoption
- Foster care
- Choosing to not have children

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Finances/Cost/Insurance Coverage?

- **NYS Mandate** (Part L of Chapter 57 of the Laws of 2019) started 1/1/2020
- The law requires coverage for standard fertility preservation services when medical treatment would directly or indirectly cause iatrogenic infertility.
- New York Insurance Law §§ 3216(i)(13)(C), 3221(k)(6)(C), and 4303(s)(3) require individual, small, and large group insurance policies or contracts that provide hospital, surgical and medical, major medical, or comprehensive care and are delivered or issued for delivery in New York to cover fertility preservation services for people with iatrogenic infertility (not required of self funded plans)

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State Dependent Coverage

- Individual, small, and large group company (over 100 employees)
- Company is NYS based
- Not self funded companies (usually tend to have 1,000 employees or more)

- Federal government?

- Medicaid?

Self Funded Group

- Not required by law
- Self funded plans often cover not only medical, but elective fertility preservation
- **PROGYNY** - self funded, but covered

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NYS Mandate

- Standard fertility preservation services are required to be covered. (collecting, freezing, preserving, and storing of ova or sperm and other standard services that are not experimental or investigational)
- Medications -- The law requires coverage for standard fertility preservation services when medical treatment would directly or indirectly cause iatrogenic infertility. Standard fertility preservation services include using prescription drugs to collect ova.
- Cost-sharing such as deductibles, copayments, and coinsurance may be imposed on fertility preservation services as long as the cost-sharing is consistent with other benefits in the policy or contract.

NYS Mandate

- No discrimination based on age, insured's expected length of life, present or predicted disability, degree of medical dependency, perceived quality of life or other health conditions, or personal characteristics, including age, sex, sexual orientation, marital status, or gender identity.
- No limit on the duration of storage. Issurer may review the services of medical necessity
- If change to new insurance, new issuer is responsible for storage bills
- Can limit to in-network provider but if unavailable, can go to out-of-network providers

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Assistance Programs for Medications

- Pharmaceutical companies
- Patient based organizations

- Require oncologists to fill out form verifying cancer diagnosis

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Effects of Tumor Directed Therapy on Fertility

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Endocrine Dysfunction in Pediatric Cancer Survivors

- Approximately 75% of pediatric cancer survivors experience effects on quality of life
  - Thyroid disease
  - Early onset puberty (before 8 years old in females, before 9 years old in males)
  - Delay or arrest in pubertal development
  - Hypogonadism
  - Ovarian insufficiency
  - Metabolic syndrome
  - Impaired bone health
  - Infertility

Keyser E et al. Gynecologic Issues in Children and Adolescent Cancer Patients and Survivors. *American College of Obstetricians and Gynecologists*. 2018; 132(2): 67-77.

Mechanisms of Chemotherapy-induced Infertility

- Accelerate and premature depletion of germ cells (follicles, sperm)
- Damage to reproductive organs (stromal cells, glands, epithelium, tissues, nerves)
- Disruption to ovarian blood flow

Bedoschi G, Navarro, P et al. Chemotherapy-induced damage to ovary: mechanisms and clinical impact. *Future Oncology*. 2016; 12(20): 2333-2344.

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Chemotherapy with Infertility Risk in Females

Table 1. Classes of chemotherapy, their action and infertility risk.

Class of agent	Examples	Mechanism of action	Infertility risk
Alkylating agents	Cyclophosphamide Mechlorethamine Chlorambucil Busulfan Melphalan	The active metabolites form cross-links with DNA with resultant inhibition of DNA synthesis and function. DNA double strand breaks and resultant P63-mediated apoptotic death in human primordial follicles [8]	High risk
Platinum-based compounds	Cisplatin Carboplatin	Covalently binds to DNA to form intra- and interstrand DNA cross-links, leading to DNA breakage during replication. This inhibits DNA transcription, synthesis and function. Specific toxicity has not been shown in human primordial follicles	Intermediate risk
Antimetabolites	Methotrexate 5-fluorouracil Cytarabine	Inhibition of DNA, RNA, thymidylate and purine synthesis. No DNA damage in human follicles, hence not gonadotoxic	Low risk
Vinca alkaloids	Vincristine Vinblastine	Inhibition of tubulin polymerization and disruption of microtubule assembly during mitosis. This arrests mitosis during metaphase and leads to cell death. No DNA damage in human follicles, hence not gonadotoxic	Low risk
Anthracyclin antibiotics	Daunorubicin Bleomycin Adriamycin (doxorubicin)	Inhibition of DNA synthesis and function. It interferes with DAN transcription. It inhibits topoisomerase II, which leads to DNA breaks. It also forms toxic oxygen-free radicals, which induce DNA strand breaks, thereby inhibiting DNA synthesis and function. Doxorubicin induces DNA double strand breaks P63-mediated apoptotic death in human primordial follicles [8]	Low risk (except adriamycin: intermediate risk)

Bedoschi G, Navarro, P et al. Chemotherapy-induced damage to ovary: mechanisms and clinical impact. *Future Oncology*. 2016; 12(20): 2333-2344.

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Chemotherapeutic Agents with High Infertility Risks in Males and Females

Alkylating Agents	Heavy Metals
Busulfan Carmustine, dacarbazine, procarbazine Chlorambucil Cyclophosphamide, Ifosfamide Lomustine Melphalan Temozolamide Fludarabine Thiotepa	Cisplatin Carboplatin Oxaliplatin

Klipstein S et al. Fertility Preservation for Pediatric and Adolescent Patients With Cancer: Medical and Ethical Considerations. *American Academy of Pediatrics*. 2020; 145(3).

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Chemotherapeutic Agents Infertility Risks in Males

Risk Level	Alkylating Agents	Antimetabolites	Anthracyclines
Intermediate Infertility Risk	Thiotepa Cisplatin < 600 mg/m2 Dacarbazine	Cytarabine Gemcitabine Hydroxyurea (long-term use)	Doxorubicin Idarubicin Daunorubicin Mitoxantrone

Risk Level	Vinca Alkaloids	Antimetabolites	Topoisomerase inhibitors	Antitumor antibiotics
Low Infertility Risk	VinCRISTINE VinBLASTINE VinORELBINE	Mercaptopurine Methotrexate	Etoposide	Bleomycin Dactinomycin Mitomycin

Lambertini M, et al. Fertility preservation and post-treatment pregnancies in post-pubertal cancer patients: ESMO Clinical Practice Guidelines. *Annals of Oncology*. 2020; 1664-1678.

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Goals of Chemotherapy for Curative Intent

- Maintain dose intensity unless contraindicated
- Acute toxicities (e.g. myelosuppression, infection, N/V, mucositis, alopecia)
- Reversible toxicities do not warrant dose reductions
- Dose reductions to avoid severe and irreversible organ damage that can compromise quality of life
  - Maximum cumulative doses

Coccia P et al. Adolescent and Young Adult Oncology. *National Comprehensive Cancer Network*. 16(1); 2018; 66-97.

Markers of Fertility

- Anti-müllerian hormone (AMH)
  - Made in ovaries and regulates follicle growth (measures ovarian reserve)
  - AMH is low in amenorrhea
- Follicle-stimulating hormone (FSH)
  - Made in the pituitary gland.
  - Regulates the menstrual cycle and stimulates egg growth. Peaks during ovulation
- Luteinizing hormone (LH)
  - Made by the pituitary gland, important in egg maturation and triggers ovulation
- Estrogen and progesterone
  - Made in ovaries and peripheries, levels vary throughout the menstrual cycle. Prepares uterus for fertilization

Lambertini M, et al. Fertility preservation and post-treatment pregnancies in post-pubertal cancer patients: ESMO Clinical Practice Guidelines. *Annals of Oncology*. 2020; 1664-1678.

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Cytotoxic Chemotherapy and Effects on Female Fertility

Degree of Risk	Treatment Type/Regimen	Comments
High risk (>80%)	-6 cycles of CMF, CEF, TAC in women ≥ 40 y/o	-Significant decline in AMH -Early menopause
Intermediate risk (20-80%)	-6 cycles of CMF, CEF, TAC in women 30-39 y/o	-Significant decline in AMH -Early menopause
	-4 cycles of AC, followed by a taxane -6 cycles of DA-EPOCH in women ≥ 35 y/o -FOLFOX in women ≥ 40 y/o	-Significant decline in AMH
	-6 cycles of CHOP in women ≥ 35 y/o	-Early menopause
Low risk (<20%)	-6 cycles of CMF, CEF, TAC in women < 30 y/o	-Significant decline in AMH -Early menopause
	-4 cycles of AC in women < 40 y/o -6 cycles of DA-EPOCH in women < 35 y/o	-Significant decline in AMH
Unknown risk	-Targeted therapies (small molecule inhibitors, biologics) -Immunotherapy	Unknown outcomes

Lambertini M, et al. Fertility preservation and post-treatment pregnancies in post-pubertal cancer patients: ESMO Clinical Practice Guidelines. *Annals of Oncology*. 2020; 1664-1678.

Targeted Therapies and Effects on Female Fertility

Degree of Risk	Treatment Type/Regimen	Comments
High-risk	Bevacizumab (VEGF-inhibitor) VEGF highly expressed in normal ovarian tissue, essential for ovarian and follicular development	Prepubic women
Low-risk		Postpubic women
Low-risk	Trastuzumab, lapatinib (HER2-inhibitor)	-No effect on AMH level -Protective effect on ovarian function
High-risk	Kinase inhibitors: imatinib, dasatinib, nilotinib	-Disrupt oogenesis, follicular maturation, ovulation, ovarian cell apoptosis, ovarian release of progesterone
Unknown risk	Checkpoint inhibitors: PD1/PDL-1 inhibitors, CTLA4 inhibitors	-Endocrine disruption (hypothyroidism, hypopituitary inflammation, hypophysitis) -Potentiate DNA-damage induced by cytotoxic chemotherapy Inhibiting PD1 may disrupt normal menstrual cycles and inhibit formation of corporal luteal

Bussies P. et al. Targeted cancer treatment and fertility: effect of immunotherapy and small molecule inhibitors on female reproduction. *RDMO*. 2022; 44(1):8 1-92.

Targeted Anti-neoplastic Therapy and Fertility

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Proposed Effect of BCR-ABL TKIs on Fertility

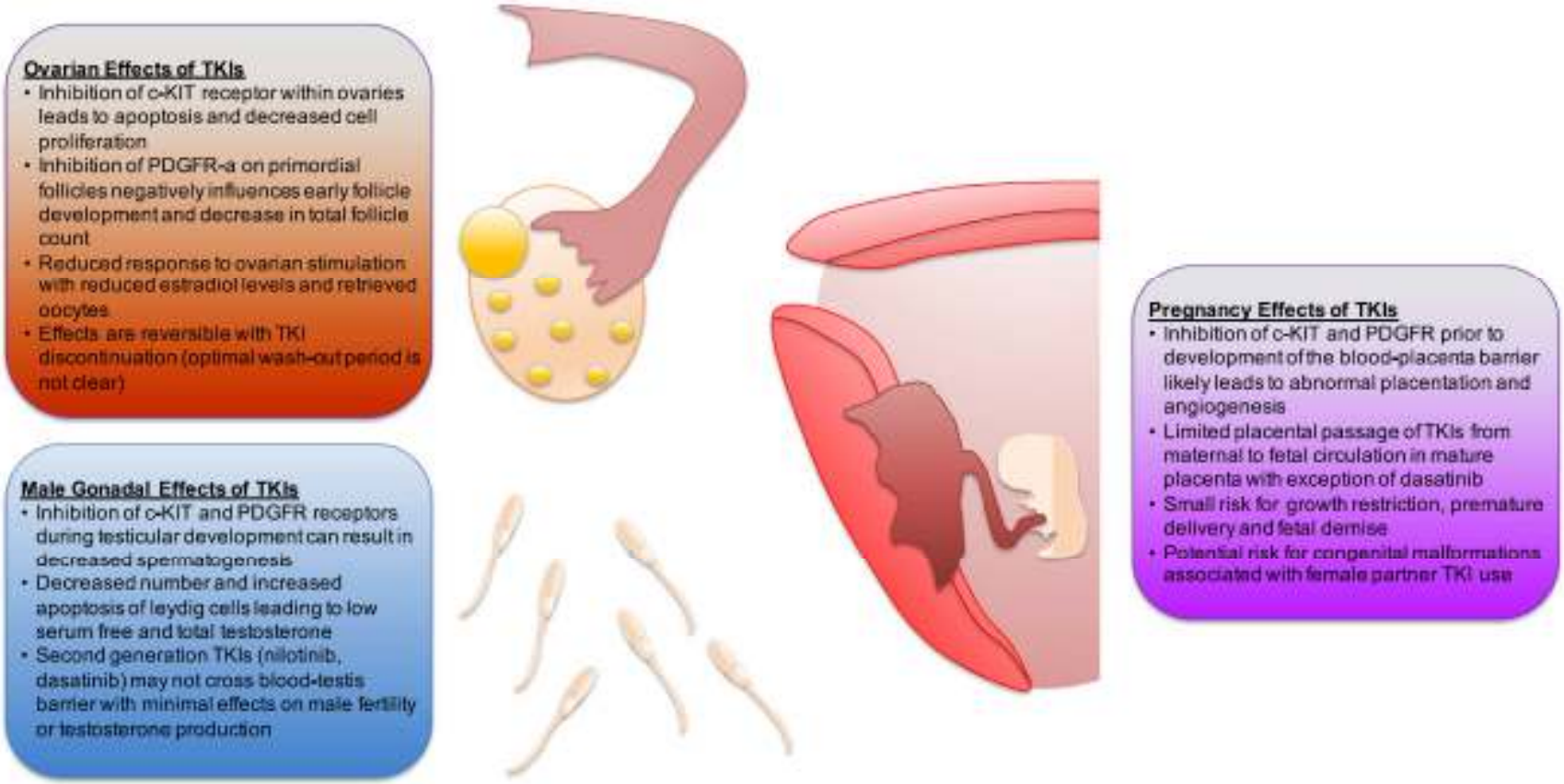

Fig. 1 Proposed impact of tyrosine kinase inhibitors on reproduction

Rambhatla A, et al. Fertility considerations in targeted biologic therapy with tyrosine kinase inhibitors: a review. *Journal of Assisted Reproduction and Genetics*. 2021; 38: 1897-1908.

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BCL-ABL Inhibitors: Female Fertility and Pregnancy

- Female CML patients receiving BCR-ABL TKIs
  - N=17 women who achieved a major molecular response (BCR-ABL transcript levels ≤ 1%)
  - Interrupted TKI therapy before or immediately after pregnancy was confirmed
  - 16 patients delivered 16 babies (11 boys, 5 girls at full term)
    - 1 spontaneous abortion with unknown fetal development
    - Median follow-up of 19 months, showed continued normal development

Dou X, et al. Planned Pregnancy in Female Patients with Chronic Myeloid Leukemia Receiving Tyrosine Kinase Inhibitor Therapy. *The Oncologist*. 2019; 24: 1141-1147.

BCL-ABL Inhibitors: Female and Male Fertility and Pregnancy

- Meta-analysis of men and women receiving a first- or second-generation BCL-ABL TKI (inhibiting c-KIT and PDGFR) at the time of conception
  - Imatinib, nilotinib, dasatinib, ponatinib, bosutinib
- Spermatogenesis heavily relies on c-KIT and PDGFR (Leydig cells)
- PDGFR is involved in primordial follicles and important for follicular development

# of Pregnancies	Term delivery without complications	Elective abortion	Spontaneous abortion	Pregnancy complications	Live births with congenital malformations
Males taking TKIs (n=236)	205 (87%)	10 (4%)	8 (3.5%)	5 (2%)	6 (2.5%)
Females taking TKIs (n=396)	186/361 (51%)	87/396 (22%)	63/396 (16%)	16/361 (4%)	20/396 (5%)

Rambhatla A, et al. Fertility considerations in targeted biologic therapy with tyrosine kinase inhibitors: a review. *Journal of Assisted Reproduction and Genetics*. 2021; 38: 1897-1908.

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BCL-ABL Inhibitors: Male Fertility

- Meta-analysis reviewed 27 articles (24) and conference abstracts (14)
  - n=374 fathers taking BCR-ABL TKIs
    - n=428 pregnancies evaluated; n=400 live births

	Pregnancies	Live births	Malformation	Delivery complications
Imatinib	327	313 (95%)	6 (1.9%)	Premature delivery (9), pregnancy hypertension, breeched baby, jaundice, neonatal respiratory distress syndrome
Nilotinib	26	26 (100%)	2 (7.7%)	Pulmonary stenosis
Dasatinib	46	43 (93%)	1 (2.3%)	Webbed fingers/toes, preeclampsia, placenta accrete
Bosutinib	16	12 (75%)	0	None reported

Szakacs Z et al. Pregnancy outcomes of women whom spouse fathered children after tyrosine kinase inhibitor therapy for chronic myeloid leukemia: A systematic review. *PLOS ONE*. 2020; 1-17.

Immunotherapy and Fertility

- Immune checkpoint inhibitors (ICI) can cause endocrine dysfunction particularly the pituitary regulates the ovaries and testes to lead to premature menopause and low testosterone levels
  - Anti-PD-1, -PDL1, -CTLA-4 agents can have direct effects on oogenesis and spermatogenesis
  - ICI's maximum toxicity during third trimester
    - Placental changes in capacity to transport immunoglobulins (IgG)

Grautti M. Checkpoint inhibitors, fertility, pregnancy and sexual life: a systematic review. ESMO Open. 2021: 6(5): 1-8.

Immunotherapy and Male Fertility

- Cross-sectional pilot study
- Male patients < 60 years old (n = 22)
- Previously treated with an immune-checkpoint inhibitor for cutaneous malignancies or uveal melanoma for at least 3 months of therapy
  - Pembrolizumab, nivolumab, ipilimumab

Low sperm count	Mean ejaculate volume	Median sperm	Sperm per ejaculate	FSH	LH	Testosterone	Other
4/22 (18%)	2 ml (1.2-8.5)	40.8 million (0-109)	116.4 million (0-364)	10.4 U/L (3.6-24.1)	3.8 U/L (2.7-8.9)	3.54 ng/ml (2.49-5.39)	5/22 (20%) autoimmune hypophysitis

Male infertility see in 2 of 22 patients (9%)

Saltzmann M. Male fertility during and after immune checkpoint inhibitor therapy: A cross-sectional pilot study. *European Journal of Cancer.* 2021: 155: 41-48.

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Fertility Preservation Recommendations

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Gonadotropin Releasing Hormone analogs (GnRHa)

- Proposed benefit to reducing ovarian tissue damage from chemotherapy
  - Inhibition of FSH-dependent accelerated follicles
  - Decrease in utero-ovarian perfusion
  - Regulates biosynthesis progesterone and dehydrogenase enzymes
- 2018 ASCO guidelines acknowledge conflicting evidence of GnRHa in preventing chemotherapy-induced ovarian failure
  - Luprolide (Lupron), Goserelin (Zoladex), Degarelix (Firmagon)
- Place in therapy: suppress menses during chemotherapy to mitigate chemotherapy-induced thrombocytopenia

Klipstein S et al. Fertility Preservation for Pediatric and Adolescent Patients With Cancer: Medical and Ethical Considerations. *American Academy of Pediatrics*. 2020; 145(3).
Oktay K et a. Fertility Preservation in Patients with Cancer: ASCO Clinical Practice Guideline Update. J Clin Oncol. 2018; 26: 1995-2001.

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GnRHa Agents

GnRH analogs	Leuprolide (Lupron, Eligard)	Goserelin (Zoladex)	Degarelix (Firmagon)
MOA	-GnRH agonist (negative feedback) -Initially increases LH & FSH, increasing testosterone (flare) and estrone/estradione, then levels decrease	-GnRH agonist (negative feedback) -Initially increases LH & FSH, increasing testosterone (flare) and estrone/estradione, then levels decrease	-GnRH antagonist -Blocks GnRH receptor to decrease LH & FSH, rapid androgen deprivation to decrease testosterone production
Monitoring Parameters	Hot flashes, ECG changes, edema, flushing, hypertension, elevated LDH/TG, weight gain, acne vulgaris		Hot flashes, elevated ALT/AST, hypertension, weight gain

Leuprolide, goserelin, degarelix. In: Lexi-drugs online [database on the Internet]. Hudson (OH): Lexicomp, Inc.; 2023.

Fertility Preservation Recommendations

- Sperm cryopreservation in postpubertal males
- Ovarian tissue cryopreservation for future transplantation may restore global ovarian function (experimental)
  - Patient does not require ovarian stimulation
  - Can be performed immediately, prior to treatment
  - Does not require sexual maturity (option in children)
- Embryo or oocyte preservation
  - An option if time and resources permitted for oocyte stimulation

Klipstein S et al. Fertility Preservation for Pediatric and Adolescent Patients With Cancer: Medical and Ethical Considerations. *American Academy of Pediatrics*. 2020; 145(3).
Oktay K et a. Fertility Preservation in Patients with Cancer: ASCO Clinical Practice Guideline Update. J Clin Oncol. 2018; 26: 1995-2001.

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Fertility Preservation Recommendations

- Menstrual suppression
  - To reduce or suppress menstruation due to chemotherapy-induced thrombocytopenia
    - GnRH analogs
      - not recommended to prevent/protect chemotherapy-induced ovarian insufficiency
    - Medroxyprogesterone
    - Oral contraceptives

Klipstein S et al. Fertility Preservation for Pediatric and Adolescent Patients With Cancer: Medical and Ethical Considerations. *American Academy of Pediatrics*. 2020; 145(3).
Oktay K et a. Fertility Preservation in Patients with Cancer: ASCO Clinical Practice Guideline Update. *J Clin Oncol*. 2018; 26: 1995-2001.
Coccia P et al. Adolescent and Young Adult Oncology. *National Comprehensive Cancer Network*. 16(1); 2018; 66-97.

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Fertility Preservation Recommendations

- In estrogen-sensitive breast cancer and gynecologic malignancies
  - Fertility preservation interventions including ovarian stimulation that increases estrogen levels may increase risk of tumor progression or cancer recurrence
- Aromatase inhibitor-based stimulation protocols have not shown increased cancer recurrence risk
  - May supplement ovarian stimulation and subsequent pregnancy

Oktay K et a. Fertility Preservation in Patients with Cancer: ASCO Clinical Practice Guideline Update. J Clin Oncol. 2018; 26: 1995-2001.

Possible Pregnancy Outcomes After Tumor Directed Therapy

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Pregnancy Risks after Chemotherapy

- Women treated with anthracycline therapy
  - Cardiac decompensation risk
- Offspring of childhood cancer survivors may risks of
  - Germline cancer from predisposed mutations
- Offspring of radiation therapy patients may have risks of
  - Premature birth and low birth weight
  - Congenital malformation
  - Genetic disorder
  - Malignancy

Keyser E et al. Gynecologic Issues in Children and Adolescent Cancer Patients and Survivors. *American College of Obstetricians and Gynecologists*. 2018; 132(2): 67-77.

Summary

- Patients of childbearing age should be counseled about fertility preservation options prior to initiating anti-neoplastic therapies
- Reproductive endocrinologists consultation can provide fertility options based on treatment goals and timelines
- Ovarian tissue cryopreservation may be an option for all females (experimental)
- Alkylating agents and platinum agents have high risk of infertility
- Small molecule inhibitors and checkpoint inhibitors have varying risks on fertility and family planning
- Patients who are planning pregnancy or who are confirmed should be monitored closely by their oncologist, REI, and OB-GYN providers

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NYSCHP September CE Webinar

Fertility Preservation Options for Oncology Patients

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