FERTILITY PRESERVATION

IN PATIENTS UNDERGOING

GONADOTOXIC TREATMENT

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INTRODUCTION

Treatment of :

- ✓ Malignancy& some precancerous conditions
- ✓ Benign conditions such as medical disorder or gender affirmation

May necessitate surgical resection of reproductive organs or administration of gonadotoxic chemotherapy or radiation therapy .

This often leads to infertility, which is a major quality of life concern.

PRETREATMENT COUNSELING

- Prior to initiating potentially gonadotoxic therapy, physicians should discuss the risk of treatment-induced infertility and possible interventions to preserve fertility .
- All patients with newly diagnosed cancer should meet with a reproductive endocrine and infertility specialist if fertility is a concern, preferably before treatment.
- The optimal approach depends upon ;

✓ The specific disease,

✓ Time available,

✓ Patient age,

✓ The type of gonadotoxic treatment (Radiation versus Chemotherapy),

✓ Whether the patient has a partner,

✓ Costs, and long-term issues (storage and use of frozen gametes or embryos).

Diseases in which affected individuals may benefit from fertility preservation interventions

Childhood cancers*	Adult cancers	Autoimmune and hematologic diseases	Benign ovarian disease
Hodgkin and non-Hodgkin lymphoma	Breast cancer	Systemic lupus erythematosus	Benign ovarian masses requiring radical surgery
Ewing sarcoma	Infiltrative ductal Stage I-III	Behçet syndrome	**Patients receiving pelvic radiation**
Pelvic osteosarcoma	Infiltrative lobular Stage IV	Steroid-resistant glomerulonephritis	Solid organ tumors presenting in the pelvis
Wilms tumor	Cancer of the cervix	Rheumatoid arthritis	Ewing's sarcoma
Genital rhabdomyosarcoma	Squamous cell carcinoma	Inflammatory bowel disease	Osteosarcoma
Burkitt lymphoma	Adeno-/adenosquamous carcinoma	Progressive systemic sclerosis	Tumors of the spinal cord
Leukemia	Infiltrative lobular[¶] Stage	Juvenile idiopathic arthritis	Retroperitoneal sarcoma
Neuroblastoma	**Malignancies of the gastrointestinal tract**	Multiple sclerosis	Rectal cancer
		Pemphigus vulgaris	Idiopathic bone disease requiring radiation
		Autoimmune thrombocytopenia	**Prophylactic oophorectomy**
	[¶]	Sickle cell disease	BRCA I and II germline mutation carriers
		Aplastic anemia	**Hematopoietic stem cell transplantation**

Chemotherapy

Chemotherapy-induced amenorrhea is a well-recognized side effect of cytotoxic chemotherapy.

- Amenorrhea is a poor surrogate for ovarian function and should not be considered as proof of menopause.
- Other factors such as :

✓ AMH<1ng/ml,

✓ FSH >10 IU (3^{rd} cycle day)

✓ Estradiol >80 pg/ml

Risk factors

There are well-recognized risk factors for chemotherapy-induced amenorrhea or ovarian failure:

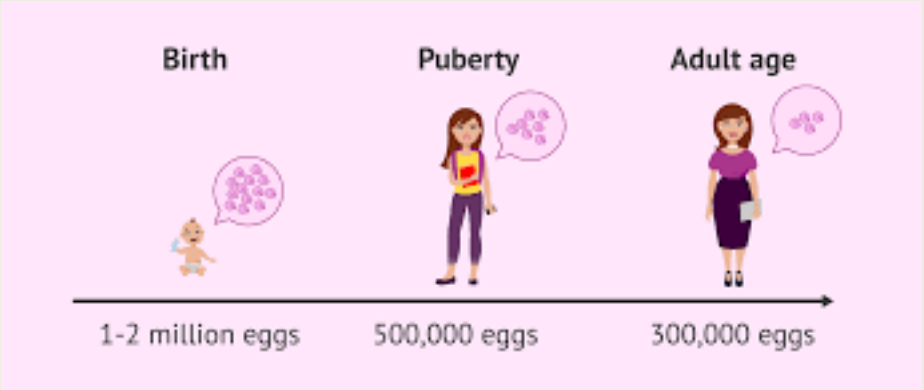
- ❑ **Age**

The risk of amenorrhea is greater in women who are over the age of 40 at the time of treatment initiation.

- ✓ Women under 30 years did not experience chemotherapy-induced amenorrhea.
- ✓ Chemotherapy-induced amenorrhea occurs in 96 % of women age 40 to 49 years.
- ✓ Ovarian function (evidenced by resumption of menses) returned in 50 percent of women younger than 40 years, but only in 10 percent of women over 40 years.

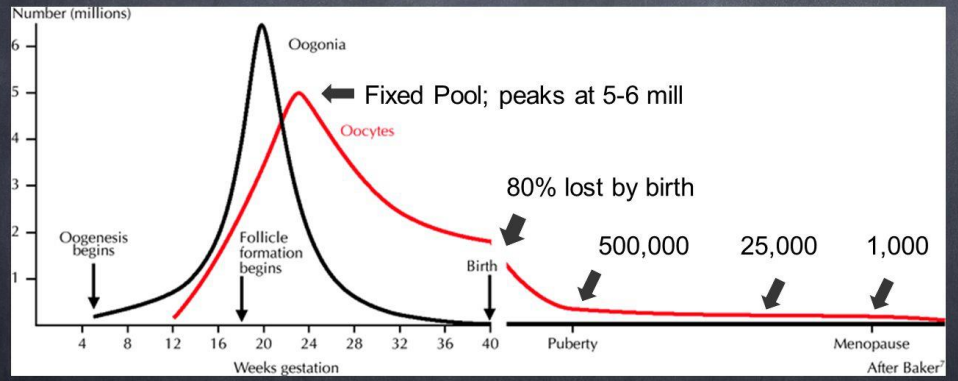
- ❑ **Chemotherapy regimen**

- ❑ **Genetic factors**



Oocyte Pool

Quantity vs. Quality



Modified from: Speroff. Clinical Gynecologic Endocrinology and Infertility. 7th ed.

Washington University in St. Louis

Chemotherapy-associated ovarian toxicity

Drug	Class (action)
Definitely associated with ovarian damage	
Nitrogen mustard	Mechlorethamine (alkylating agent)
L-phenylalanine mustard	Mechlorethamine (alkylating agent)
Chlorambucil	Chloroethylamine (alkylating agent)
Cyclophosphamide	Chloroethylamine (alkylating agent)
Melphalan	Mechlorethamine (alkylating agent)
Busulfan	Alkylalkane sulfonate (alkylating agent)
Procarbazine	Substituted hydrazine
Dacarbazine	Alkylating agent
Probably associated with ovarian damage	
Vinblastine	Vinca alkaloid
Cytosine arabinoside (Ara-C)	Antimetabolite
Cis-platinum	Heavy metal
Carmustine	Nitrosourea (alkylating agent)
Lomustine	Nitrosourea (alkylating agent)
VP-16 (etoposide)	Podophyllotoxin
Imatinib	Tyrosine kinase inhibitor
Low probability of ovarian damage	
Methotrexate	Antimetabolite
Fluorouracil (5-FU)	Antimetabolite
6-mercaptopurine	Antimetabolite
Vincristine	Vinca alkaloid
Mitomycin	Antibiotic (alkylating agent)
Unknown	
VM-26	Podophyllotoxin
Daunorubicin	Anthracycline
Bleomycin	Peptide
Vindesine	Vinca alkaloid
Doxorubicin	Anthracycline

Radiationtherapy

- Oocyte Radiosensivity is <2Gy
- The dose of radiotherapy that would result in immediate and permanent ovarian failure in 97.5 present of patients

- ✓ 20.3 Gy at birth
- ✓ 18.4 Gy at age 10 years
- ✓ 16.5 Gy at age 20 years
- ✓ 14.3 Gy at age 30years

Radiation doses and risk of gonadal failure
(High risk: > 80% sterilized; Mild risk: 20–80% sterilized; Low risk: < 20% sterilized)

Radiation Doses	Risk of Ovarian Failure		
	Prepubertal girls	15–40 years	> 40 years
Pelvic/abdominal irradiation			
< 6Gy	Mild risk	No adverse effects	No adverse effects
15 Gy	High risk	Low risk	Mild risk
25–50 Gy	High risk	Mild risk	High risk
50–80 Gy	High risk	Mild risk	High risk
> 80 Gy	High risk	High risk	High risk
Cranio-spinal irradiation > 25 Gy	Mild risk	Mild risk	Mild risk
Total body irradiation	High risk	High risk	High risk

FERTILITY PRESERVATION

Cryopreservation

- ❑ Semen : successful and robust
- ❑ Oocyte : technically difficult but useful for:
- ✓ Creating donor egg banks
- ✓ Preserving fertility in young cancer survivors
- ✓ Preserving fertility in women deferring reproduction

- ❑ Gonadal tissue

The presence of cancer probably does not affect ovarian reserve or responsiveness to gonadotropins prior to gonadotoxic therapy.

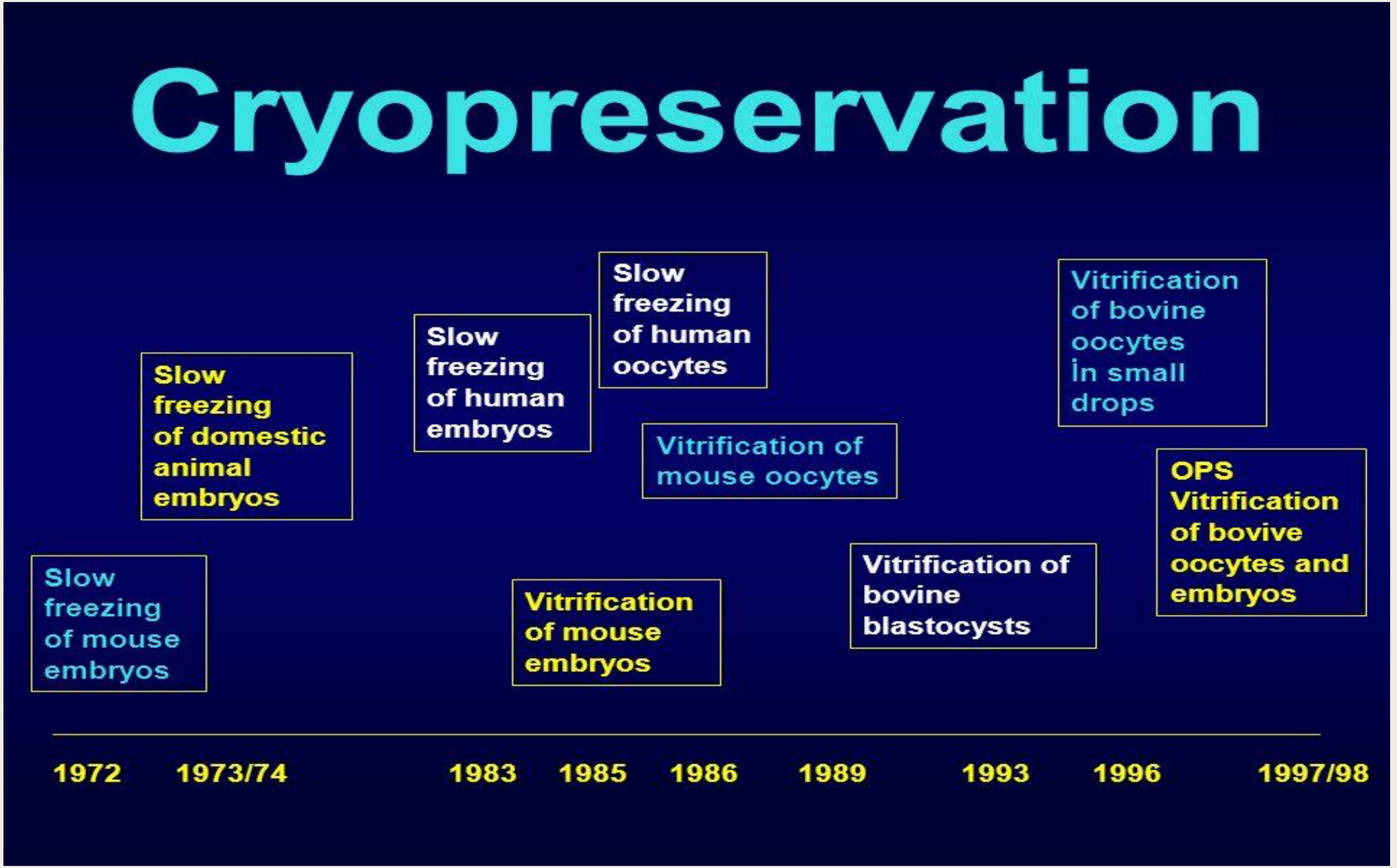
ASSESS PATIENT GOALS FOR THERAPY

- For prepubertal children investigational techniques include possible gonadal cryopreservation.
- Cryopreservation of embryos or gametes is the established method of fertility preservation for adults and post pubertal children.
- Use of GNRH agonists during chemotherapy

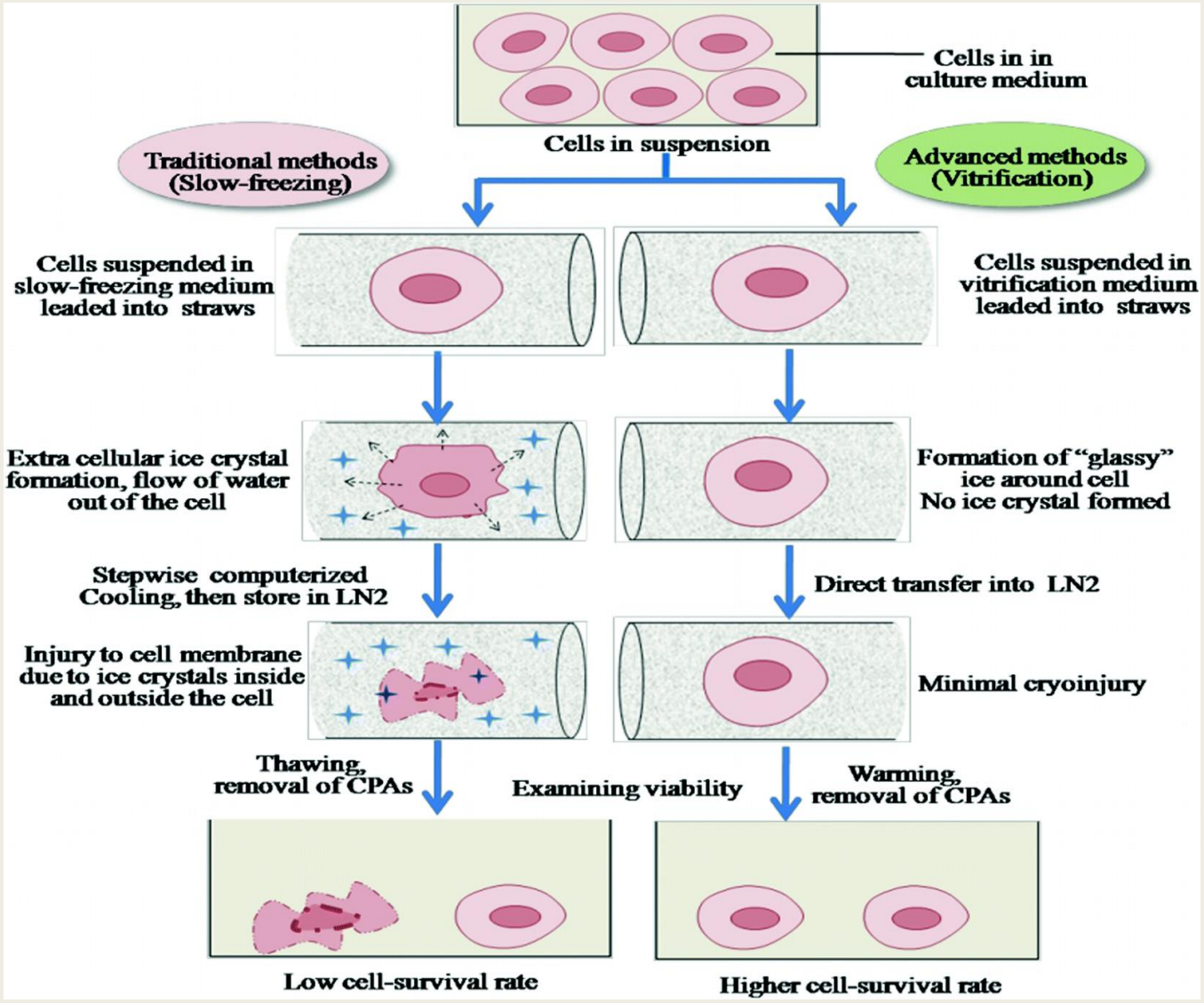
✓ Live birth rate is lower than proven ART technology

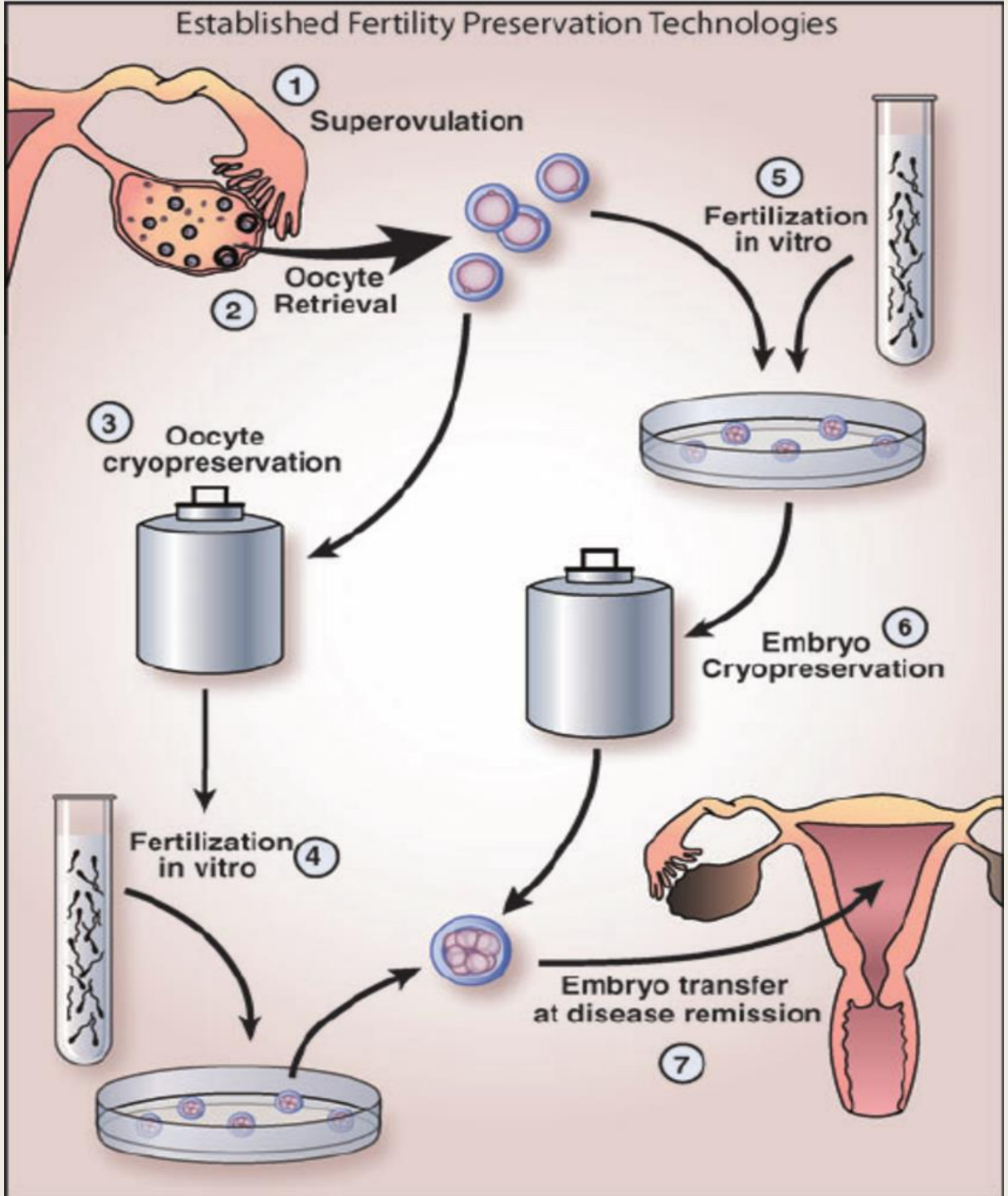
✓ It does not preserve fertility in men

Cryopreservation

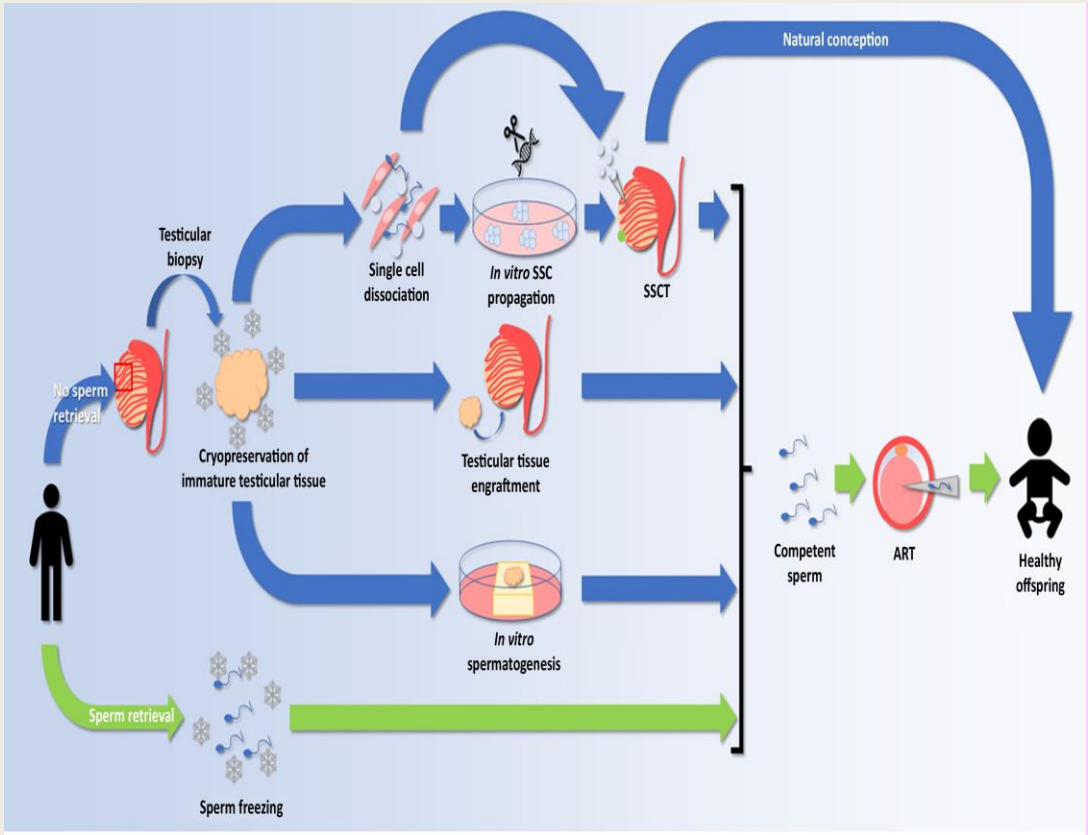


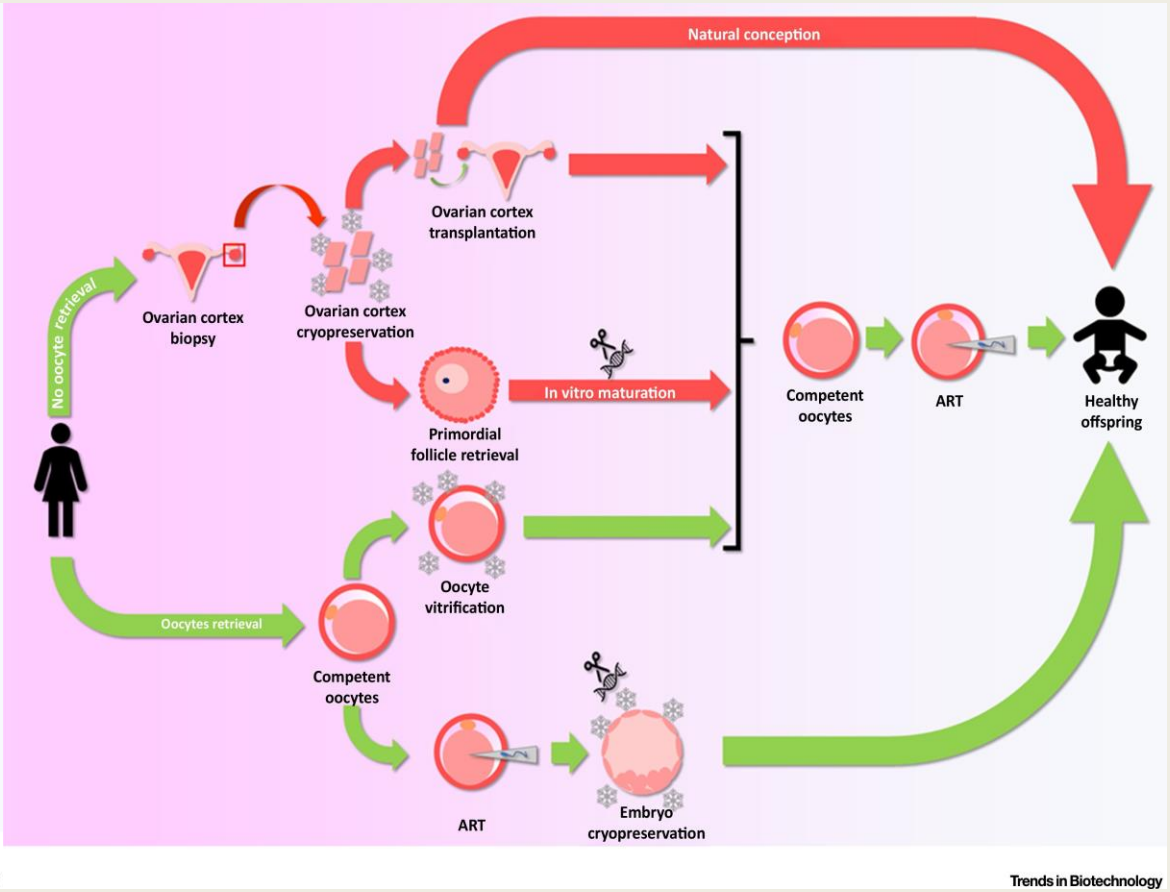
Gamete cryopreservation




Established Fertility Preservation Technologies
1
Superovulation
2
Oocyte
Retrieval
3
Oocyte
cryopreservation
4
Fertilization
in vitro
5
Fertilization
in vitro
6
Embryo
Cryopreservation
Embryo transfer
at disease remission
7

TISSUE CRYOPRESERVATION





OTHER METHODS TO PRESERVE OR RESTORE FERTILITY

- Radical Trachelectomy for cervical cancer
- Hormonal therapy for early stage endometrial cancer
- Egg donation(fresh or frozen donor oocyte +partner's sperm can be used for IVF with success rates exceeding 60% per embryo transfer).
- Embryo donation
- Gestational carrier
- Adoption
- Uterus transplantation

OVARIAN HORMONE PRESERVATION

- For women who desire only potential preservation of ovarian hormone production:
- ✓ Premenopausal women with completed childbearing
- ✓ Women in whom established cryopreservation procedures are not an option

- Some practitioners discuss GNRH agonists to suppress ovarian function
- ✓ If used ,it should be coadministered during treatment
- ✓ It can not replace established methods of fertility preservation
- ✓ It can not be used for preservation of testicular hormone production .

Women with heavy menstrual bleeding

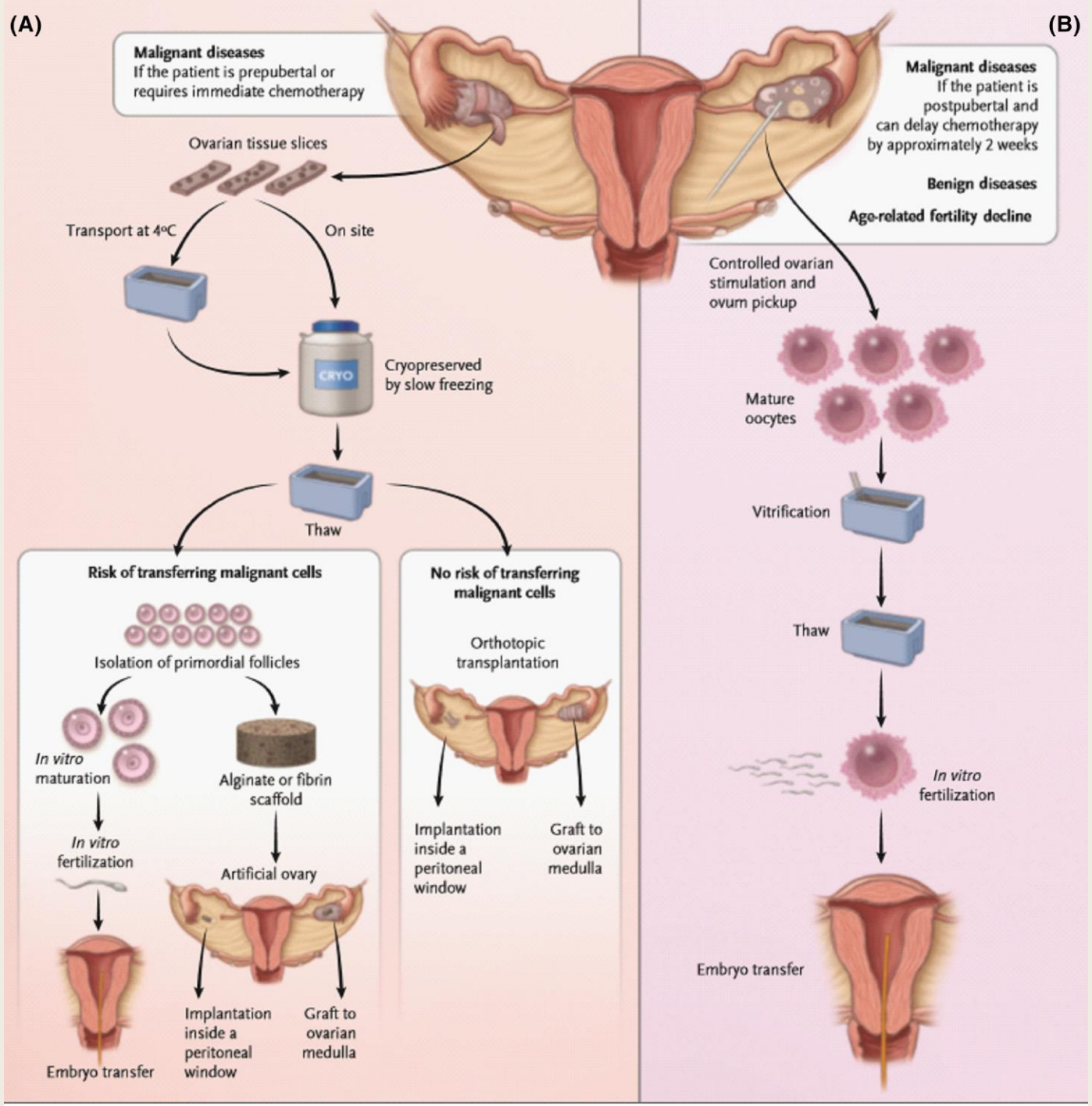
- ✓ We do use GNRH agonist to prevent menorrhagia in women at risk of sever chemotherapy- induced thrombocytopenia.
- ✓ If possible it should be initiated 2-3 weeks before therapy and continued until the end of chemotherapeutic treatment.
- ✓ Side effects include hot flushes and vaginal dryness

RADIATION –SPARING APPROACHES

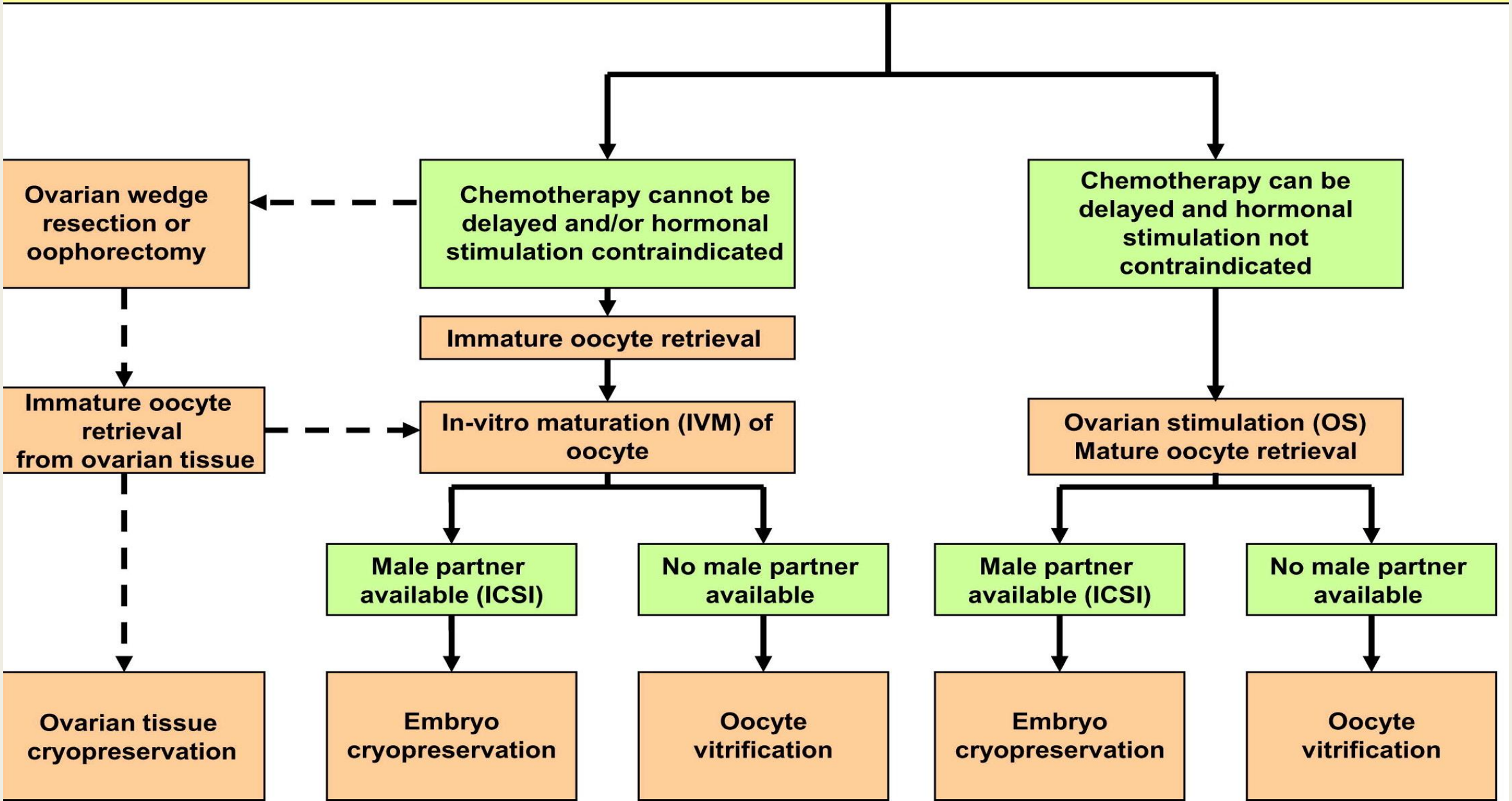
- Ovarian radiation can result in atrophy and decreased follicle number.

- The degree of ovarian damage depends upon the patients age and the dose of radiation delivered to the ovaries and can be compounded by the addition of chemotherapy.

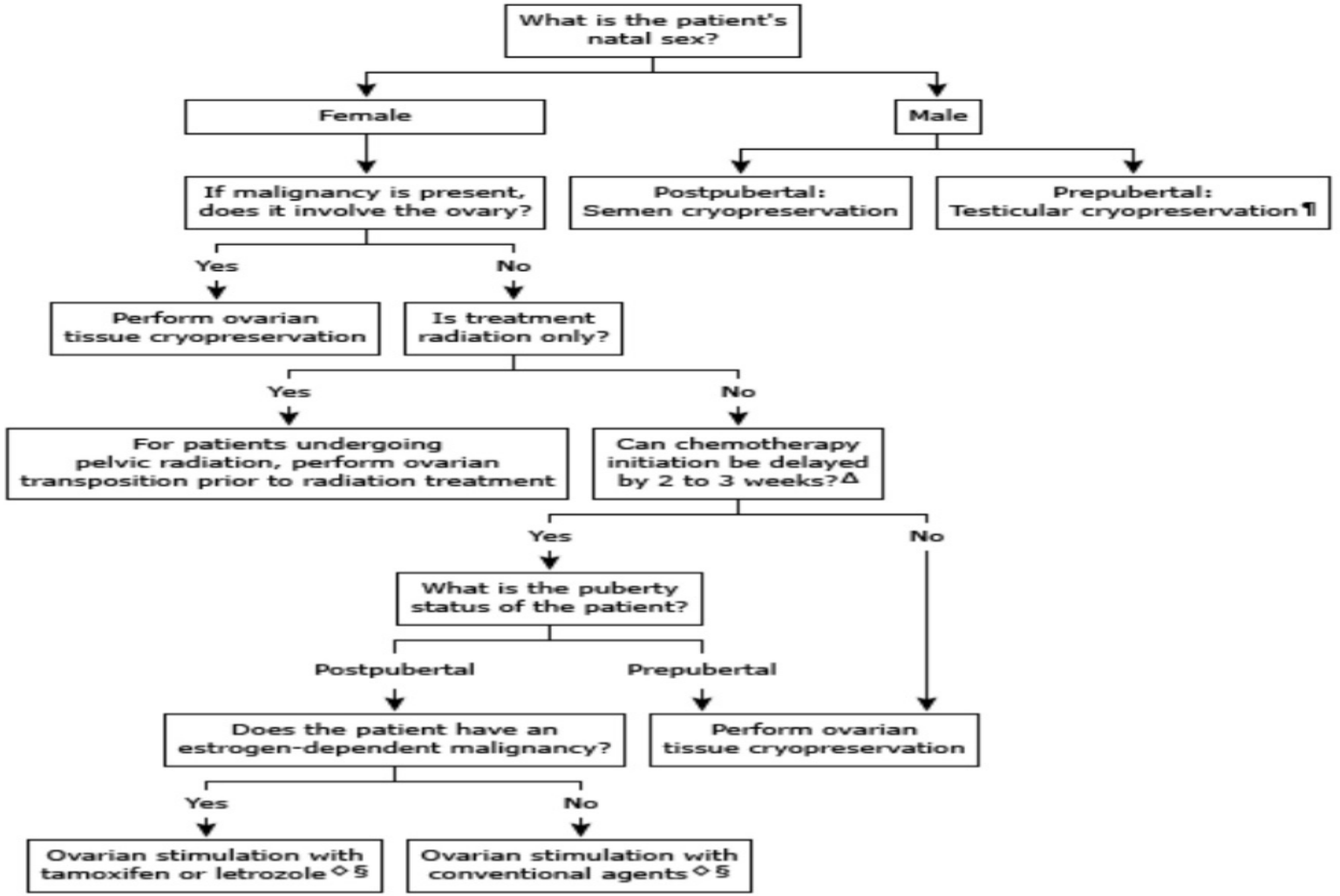
- Transposition(oophoropexy)
- Shielding
- Autotransplantation

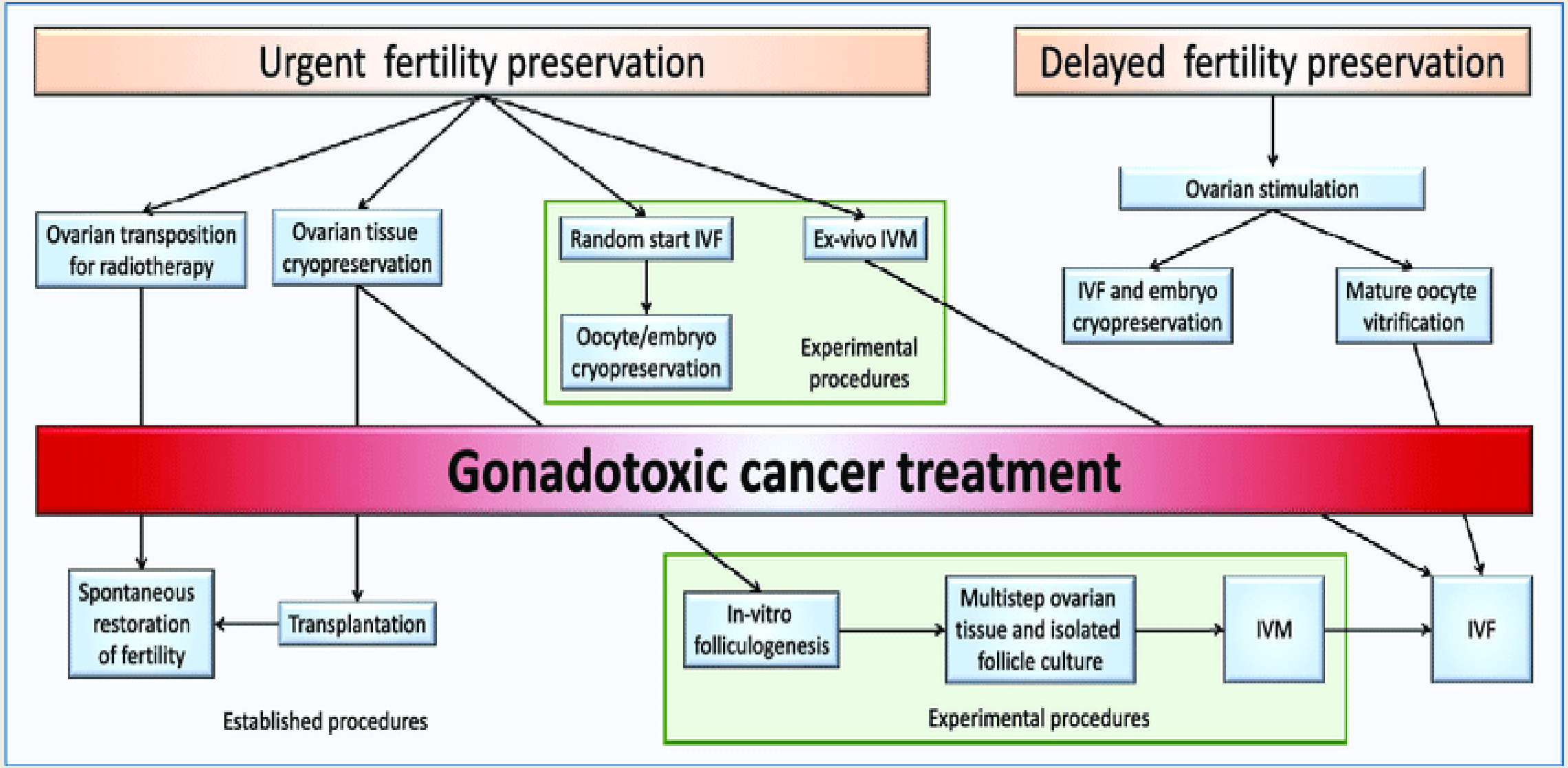

(A)
Malignant diseases
If the patient is prepubertal or requires immediate chemotherapy
Ovarian tissue slices
Transport at 4°C
On site
CRYO
Cryopreserved by slow freezing
Thaw
Risk of transferring malignant cells
Isolation of primordial follicles
In vitro maturation
In vitro fertilization
Embryo transfer
Alginate or fibrin scaffold
Artificial ovary
Implantation inside a peritoneal window
Graft to ovarian medulla
No risk of transferring malignant cells
Orthotopic transplantation
Implantation inside a peritoneal window
Graft to ovarian medulla
(B)
Malignant diseases
If the patient is postpubertal and can delay chemotherapy by approximately 2 weeks
Benign diseases
Age-related fertility decline
Controlled ovarian stimulation and ovum pickup
Mature oocytes
Vitrification
Thaw
In vitro fertilization
Embryo transfer

Fertility preservation strategies offered to female cancer patients



Approach to fertility preservation for patients undergoing gonadotoxic therapy*




Urgent fertility preservation
Delayed fertility preservation
Ovarian stimulation
Ovarian transposition for radiotherapy
Ovarian tissue cryopreservation
Random start IVF
Ex-vivo IVM
IVF and embryo cryopreservation
Mature oocyte vitrification
Oocyte/embryo cryopreservation
Experimental procedures
Gonadotoxic cancer treatment
Spontaneous restoration of fertility
Transplantation
In-vitro folliculogenesis
Multistep ovarian tissue and isolated follicle culture
IVM
IVF
Established procedures
Experimental procedures

Thanks for your attention.


THANK YOU
FOR YOUR ATTENTION