پژوهشگاه فناوری‌های نوین علوم زیستی جهاد دانشگاهی ابن سینا

In the name of God

Strategies for Fertility Preservation in Patients Cancer

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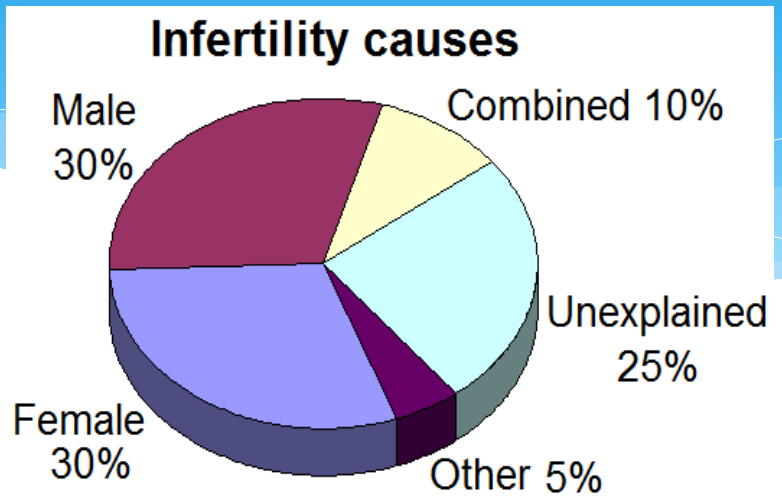
Incidence of Infertility

- 15 – 20% of couples infertility



- ***Causes of infertility***
  - *Anatomical defects*
  - *Physical problems*
  - *Endocrine disorders*
  - *Genetic disorders*
  - *Diseases (**Cancer,** Immunology, Infection, Diabetes,…)*
  - *Environmental (lifestyle problems, Radiation, Drug abuse, psychological)*

Introduction

* Over 1.5 million people who were diagnosed as having cancer about 4% of patients are under the age of 35 years

* With efficacy cancer treatment include chemotherapy, radiotherapy or bone marrow transplantation a many of patients can achieve long-term survival, but fertility can be temporarily or permanently affected by cancer in various ways

* The disease process as well as treatments of cancer can impair the hypothalamic pituitary-gonadal axis, the structural and functional integrity of the germinal epithelium, and female and male sexual function

* Infertility related to cancer is a major issue for many cancer survivors, although infertility most commonly occurs as the result of treatment cancer with *gonadotoxic agents*, disorder of *fertility related to cancer can manifest before, during or after treatment*

Introduction

* Fertility preservation is an field that offers treatment aimed at protecting future reproductive ability for individuals with cancer, other serious illnesses

* Fertility preservation strategies vary by patient *age and sex*

* The only possibility to preserve the patient's fertility is allow patients to store *gametes, gamete stem cells or reproductive tissues* for potential future use to create offspring

* For the *prepubertal* patient, cryopreservation of sperm and oocyte is *impossible*. Research primarily in animal models into promising fertility preservation and restoration strategies might provide a clinical solution in the future

* Promising advances in *spermatogonial stem cell (SSCs)* research might lead to future fertility preservation and restoration options for male patients with cancer

* Patients rendered infertile by cancer treatments who did not cryopreserve gametes before and are unable to father a biological child

Etiology of Cancer-Induced Infertility

* The modern approach to cancer management has evolved into a multidisciplinary initiative focused not only on cancer specific and *overall survival, but also patient quality of life*

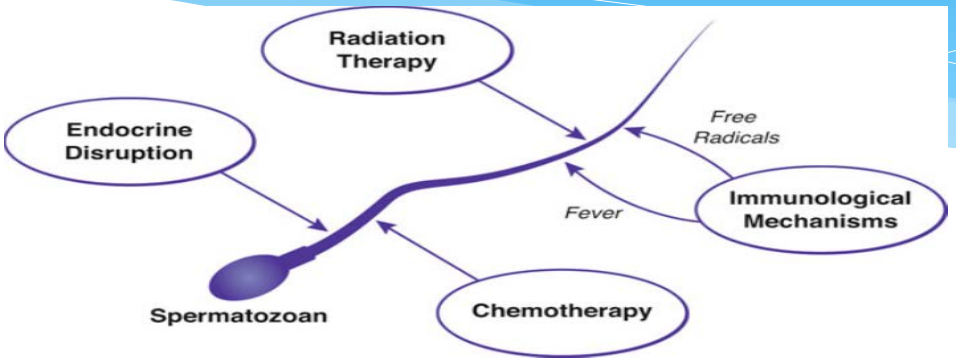
* The *oncofertility* (biomedical community) faces several main challenges related to the preservation of fertility in people with cancer
  - *The improvement of patient-specific*
  - *Life-preserving treatments*
  - *The identification & reduction of the threat that cancer treatment cases to fertility*

* Preservation of *gonadal function* is an important priority for the long-term health of cancer survivors of *both sexes and all ages at treatment*

* Etiology of cancer related infertility enables the treating physician to effectively counsel patients and plan therapy to optimize for successful fertility preservation

Etiology of Cancer-Induced Infertility

* Infertility associated with cancer may occur secondary to numerous factors, including the *primary cancer itself, surgery, radiation, chemotherapy, or a combination*



* The most common cancers in male & female:
  - ✓0–19 years of age are leukemia's and central nervous system (CNS) tumors
  - ✓20–44 years of age, testicular cancer, breast, melanoma, and non-Hodgkin lymphoma, cervical cancer
  - ✓>45 years, prostate, lung, and colorectal cancers are seen most often

* A wide of therapeutic are used to various cancers affecting men & female of reproductive age that each treatment is associated with risk of reproductive harm

Primary Cancer

* Some cancers, by itself, may have a *direct effect on fertility* include:
  - *Impaired semen quality* in patients with leukemia, lymphoma, and testicular cancer
  - Some patients with cancer present with baseline *oligospermia, azoospermia, or sperm chromosomal aneuploidy , destroy follicles & premature ovarian failure*
  - Many men will recover sperm production within one to three years after treatment is and some may have permanent azoospermia, or absence of sperm
* The *primary cancer or the immune response* to the cancer as a helper factor to damaged male and female fertility in these patients cancer
* ***Factors for cancer induced infertility likely include***
  - *A systemic inflammatory state an increased immune response, tumor and cytokine release*
  - *Febrile status*
  - *Multiple system disorders resulting from the chronic disease state*
  - *Malnutrition*
  - *Affected by variations in systemic hormones*
  - *Hormonally mediated mechanisms(testicular germ cell tumors & hematopoietic cancers)*
  - *Decreased hormones due to a direct systemic stress or indirectly metabolic*

Clinical Evaluation

* In addition to the challenges associated with a new diagnosis of cancer, young patients in particular are faced with the *long-term distress of possible future infertility*

* The *loss of fertility* may have either a perceived or real impact on a patient's *physical, economic, social, and sexual life*. Concerns regarding infertility are second only to questions regarding mortality in this group

* A majority of 13–21-year-old cancer survivors surveyed indicated their willingness to participate in *fertility preservation* had it been offered, further highlighting the importance of the issue

Surgical treatment

* Surgical treatment for cancer is another *potential cause of fertility disorder*

* Orchiectomy is currently the standard of care for diagnosis and initial management of *primary testicular germ cell tumors*, and it may occasionally be performed for treatment of other cancers such as prostate cancer

* Surgery may alter the ability to natural ejaculation *by damaging the neurologic or functional mechanism of sperm delivery*

* Despite improvements, select surgical procedures can result in the *loss of ability to fertility naturally*, thus necessary the use of assisted reproductive techniques (ART)

Chemotherapy

Chemotherapeutic drugs act by interrupting vital cell processes and arresting the normal cellular proliferation cycle, damaging effect on the germ cells

* They cause DNA abnormalities as well as oxidative damage in somatic and germ cells & the testis is more sensitive to chemotherapy than the ovary

* Chemotherapeutic agents have *a wide and variable range of impact on female and male fertility*

* The cytotoxic affects are dependent on the types of cytotoxic drugs, the dosage of the drugs and also the age of the women & male

* *Alkylating agents* such as cyclophosphamide, chlorambucil, busulfan are associated with the *greatest risk of gonadotoxicity* that impede spermatogenesis in a dose-dependent manner
* whereas *antimetabolites*, platinum-based agents, vinca alkaloids, topoisomerase inhibitors are also noted to *be gonadotoxic*

Chemotherapeutic agents

- Risk of Infertility with chemotherapeutic agents include: *High Risk, Intermediate Risk, Low Risk, Very Low / No Risk, Unknown Risk*

- Most *cytotoxic* forms of chemotherapy are not *tumor specific and target* rapidly *dividing cell types*

- MOPP=mechlorethamine/oncovin (vincristine)/procarbazine/prednisone
- MVPP=mechlorethamine/vinblastine/procarbazine/prednisolone
- COPP=cyclophosphamide/oncovin/procarbazine/prednisone
- ChlVPP=chlorambucil/vinblastine/procarbazine/prednisolone
- EVA=etoposide/vinblastine/adriamycin (doxorubicin)
- ABVD=adriamycin/bleomycin/vinblastine/dacarbazine
- BEP= bleomycin/etoposide/cisplatin
- OEPA=oncovin/etoposide/prednisone/adriamycin (doxorubicin)
- NOVP=novantrone (mitoxantrone)/oncovin/vinblastine/prednisone
- CHOP=cyclophosphamide/hydroxydaunomycin/oncovin/prednisone
- COP=cyclophosphamide/oncovin/prednisone

Radiation

The size of Ovary and testicular damage sustained by radiation therapy is *directly related both to* ***the dose*** *of radiation delivered as well as the* ***underlying cell type***

* *Seminiferous tubules* are particularly *sensitive to radiation* with energies as low as 0.1 gray (Gy), resulting in *temporary arrest of spermatogenesis*

* *Increasing doses radiation to cause azoospermia* at 0.65 Gy with doses of <1 Gy, 2–3 Gy, and 4–6 Gy, resulting in azoospermia lasting 9–18 months, 30 months, and 5 years to *permanent*, respectively

* *Damage to seminiferous tubules,* radiation to directly result in injury to other *testicular cell types including DNA fragmentation in sperm,* when considering ART in patients who previously received testicular radiation

* the sensitivity of an oocyte/follicle to radiation induced *apoptosis/atresia* may widely differ between species *or between follicular stages*.
* The dose necessary to destroy 50 % of primordial follicles (LD 50) would be, 2 Gy , mature cells take the onslaught of the effect of radiotherapy

Radiation and Chemotherapy Mechanism

* Both radiation and chemotherapy can result in damage to the destroy spermatogonial germ cells, *seminiferous tubules, including spermatogonial cells and Sertoli cells, destroy follicles (each containing a single oocyte or egg), causing premature ovarian failure, with subsequent infertility and early menopause .breast, ovary,* with resultant detrimental effects on fertility

* Low levels of gonadal toxicity can result in damage to stem cells

* High doses of gonad toxic therapy may cause apoptosis cells resulting in reduction of stem cells and stable infertility

* In contrast to the seminiferous epithelium, Leydig cells are relatively resistant to both *radiation and chemotherapy*, and cancer treatments rarely result in clinical hypogonadism

* This susceptibility to radiation and chemotherapy occurs not only after initiation of spermatogenesis but throughout all ages, including before puberty

* The direct toxic effects of chemotherapy and radiation exposure on the gonads is generally *dose-dependent*

Combination Therapies

* As many cancers are commonly treated with *combination therapies of chemotherapeutic agents and in conjunction with radiation therapy*, it is difficult to determine the effects of individual treatments on *overall fertility*

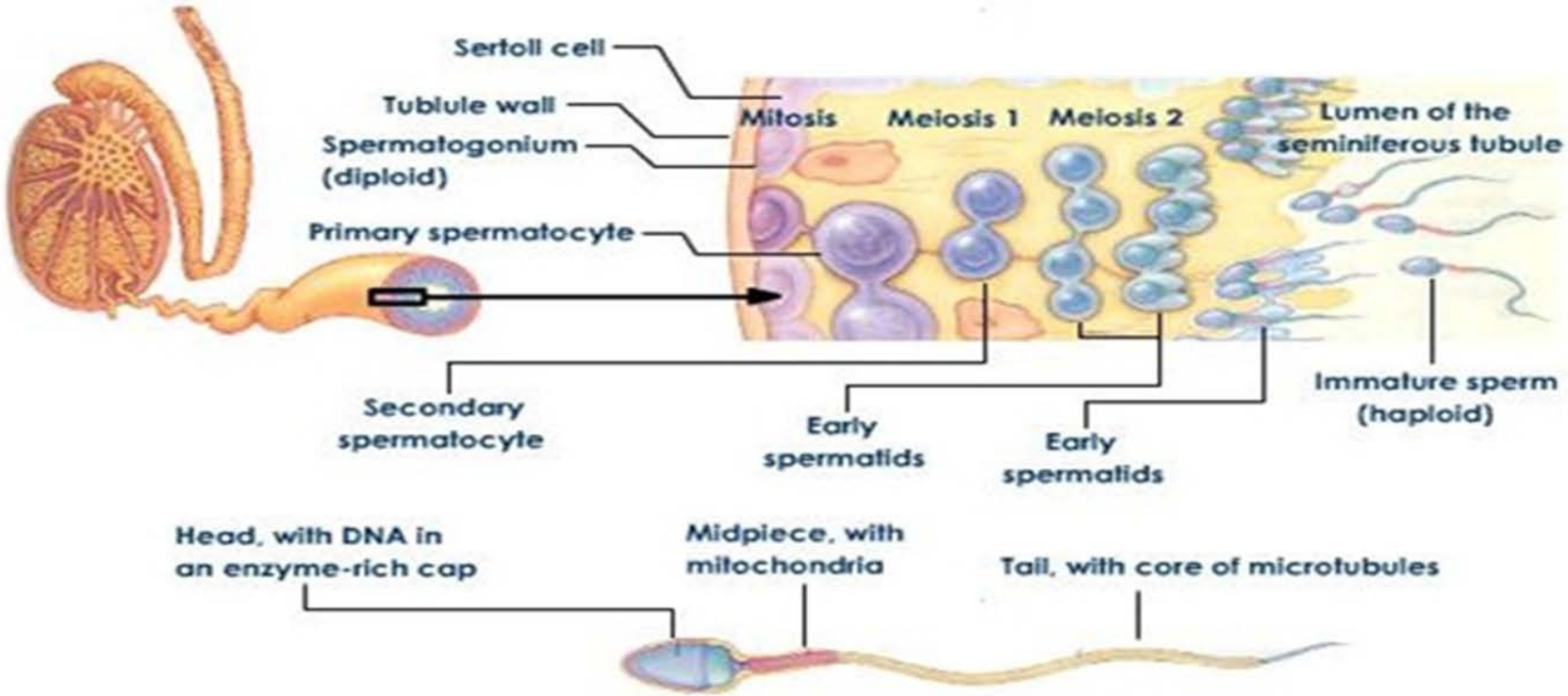
* It is *often difficult to identify the specific impact of individual drugs, given the frequency of combination therapies*

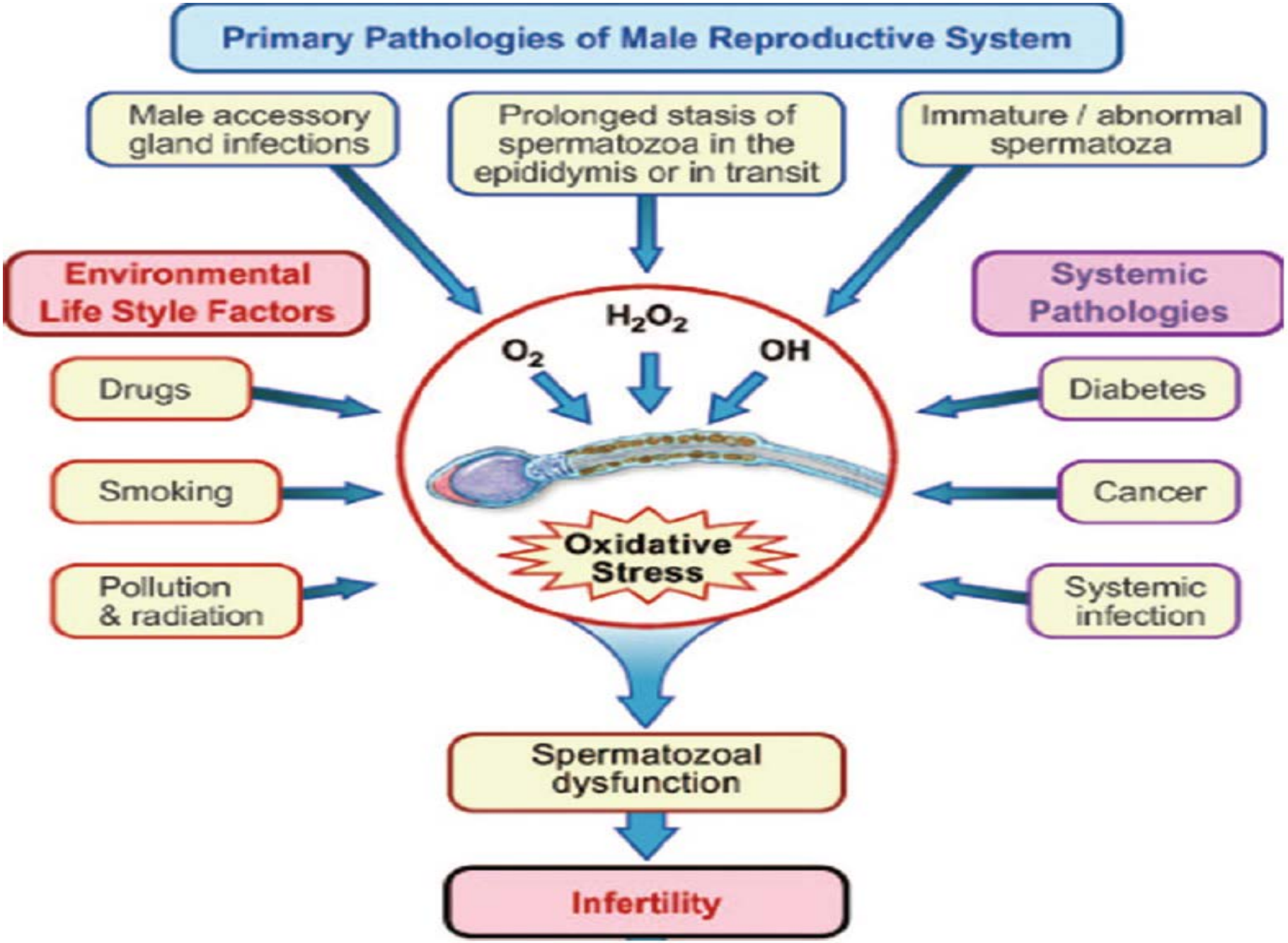
* Similarly, patients with acute lymphoblastic leukemia undergoing chemotherapy and radiation therapy were found to have *spermatogonia present in fewer than 40% of seminiferous tubule*

Stages of spermatogenesis from spermatogonia sperm production

- Spermatogenesis is one of the most crucial stages in male fertility (74 days).The smallest error in the natural course of spermatogenesis can lead to infertility in men
- The regulation of spermatogenesis occurs in two main stages:

  1) hormonal and endocrine 2) paracrine and autocrine




Primary Pathologies of Male Reproductive System
Male accessory gland infections
Prolonged stasis of spermatozoa in the epididymis or in transit
Immature / abnormal spermatoza
Environmental Life Style Factors
Systemic Pathologies
H_2O_2
O_2
OH
Drugs
Smoking
Pollution & radiation
Diabetes
Cancer
Systemic infection
Oxidative Stress
Spermatozoal dysfunction
Infertility

Fertility Preservation before Cancer Treatme

* Cryopreservation gametes is a process where cells or whole tissues are preserved by cooling to low sub-zero temperatures, such as (typically) −196 °C (the boiling point of liquid nitrogen).

* At these low temperatures, any biological activity, including the *biochemical reactions that would lead to cell death, is effectively stopped.*

Fertility preservation options in male

- Fertility preservation in males depends on the *sexual maturity* of the patient

- All patients undergoing gonadotoxic therapy should be offered *sperm cryopreservation,* some patients will be able to recover from gonadotoxic

- Counseling all males about the reproductive risks of cancer treatment and availability of fertility preservation options prior to initiation of cancer therapy and consideration of referral to a reproductive urologist is recommended

- Post pubertal males should be offered sperm cryopreservation as this is the standard fertility-preservation method

- Cryopreservation of spermatogonia may be performed by testicular biopsy in prepubertal boys where spermatogenesis has not yet commenced. Testicular biopsy can produce psychological trauma to young boys and also cause anxiety in parents

Fertility preservation options in male

* Sperm cryopreservation should be considered for *all patients prior to cancer therapy*, ultimately, some patients are fortunate and recover sufficient levels of spermatogenesis post treatment to sustain normal fertility

* Sperm banking provide both a *sense of security and reassurance of the future*, many patients that sperm banking is a method of coping with cancer preserving future fertility, *even if the samples remain unused*

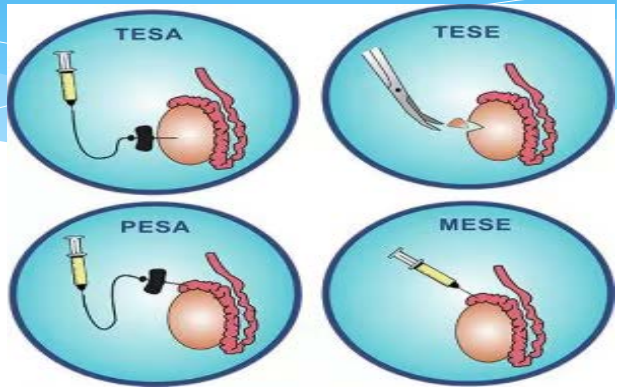
* Semen collection should be performed prior to the administration of gonadotoxic therapies such as chemotherapy or radiation therapy

* *Several samples are typically collected due to frequently reduced semen quality* in cancer patients, and samples are obtained prior to cancer treatment to ensure *optimal DNA integrity and sperm quality*

Testicular Tissue Cryopreservation

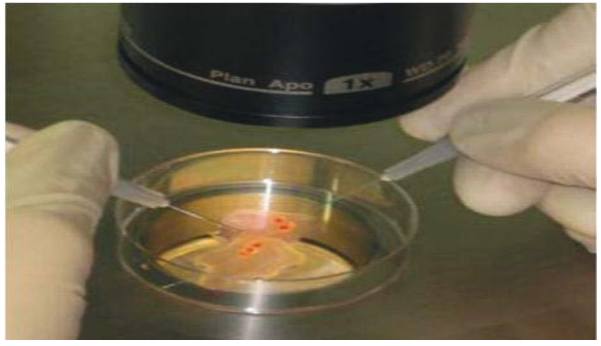
* *Anatomic obstruction* (absencobstruction, etc.), sperm can be obtained via *multiple techniques that sperm can be frozen* for future :

  - *Microsurgical epididymal sperm aspiration (MESA)*
  - *Percutaneous epididymal sperm aspiration (PESA)*
  - *Testicular sperm extraction (TESE)*
  - *Testicular sperm aspiration (TESA or micro-TESE)*



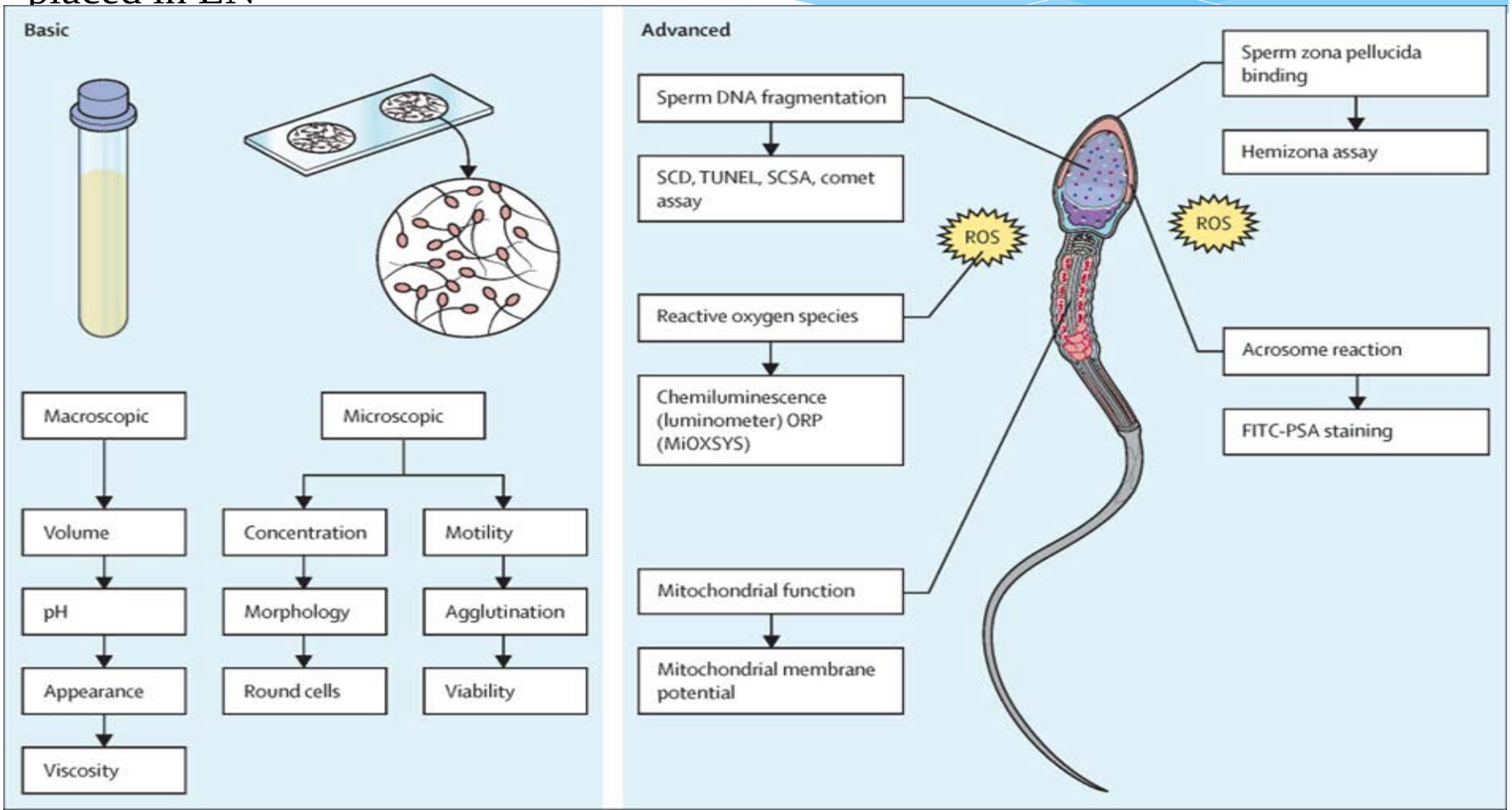
* For prepubertal patients who have not initiated spermatogenesis, cryopreservation of testicular tissue through either *cell suspension or whole tissue as a possible option for fertility preservation*

* The hope is that one day technology will evolve to permit successful use of this immature, cryopreserved, testicular tissue in ART

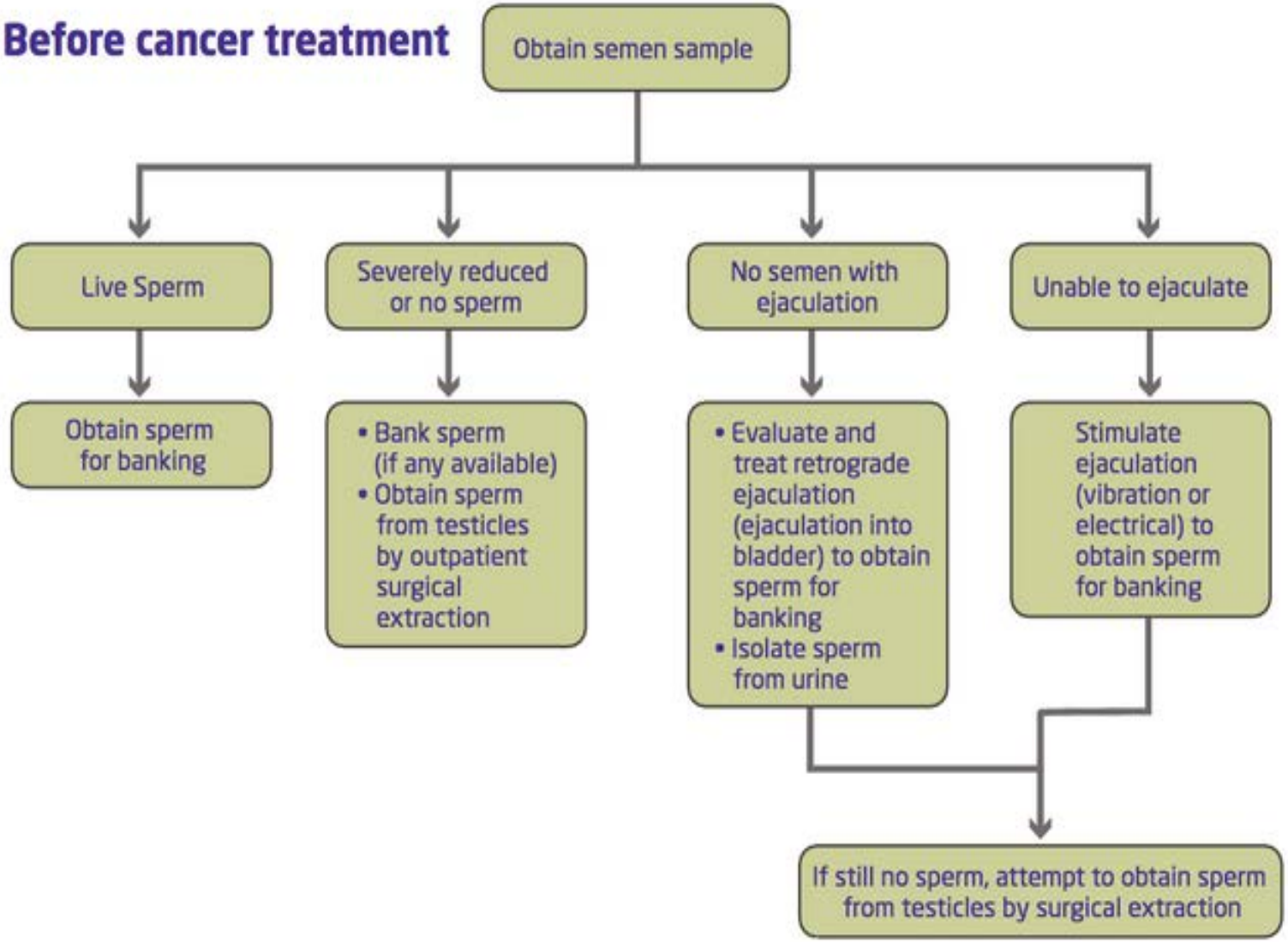


Sperm preservation

* Sperm cryopreservation is currently performed using slow-rate cryopreservation as a standard method, in which sperm cells are incubated with a cryoprotective medium and slowly subjected to hypothermia in liquid nitrogen (LN) vapor before they are placed in LN



Before cancer treatment



During cancer treatment

Radiation shielding of the testes

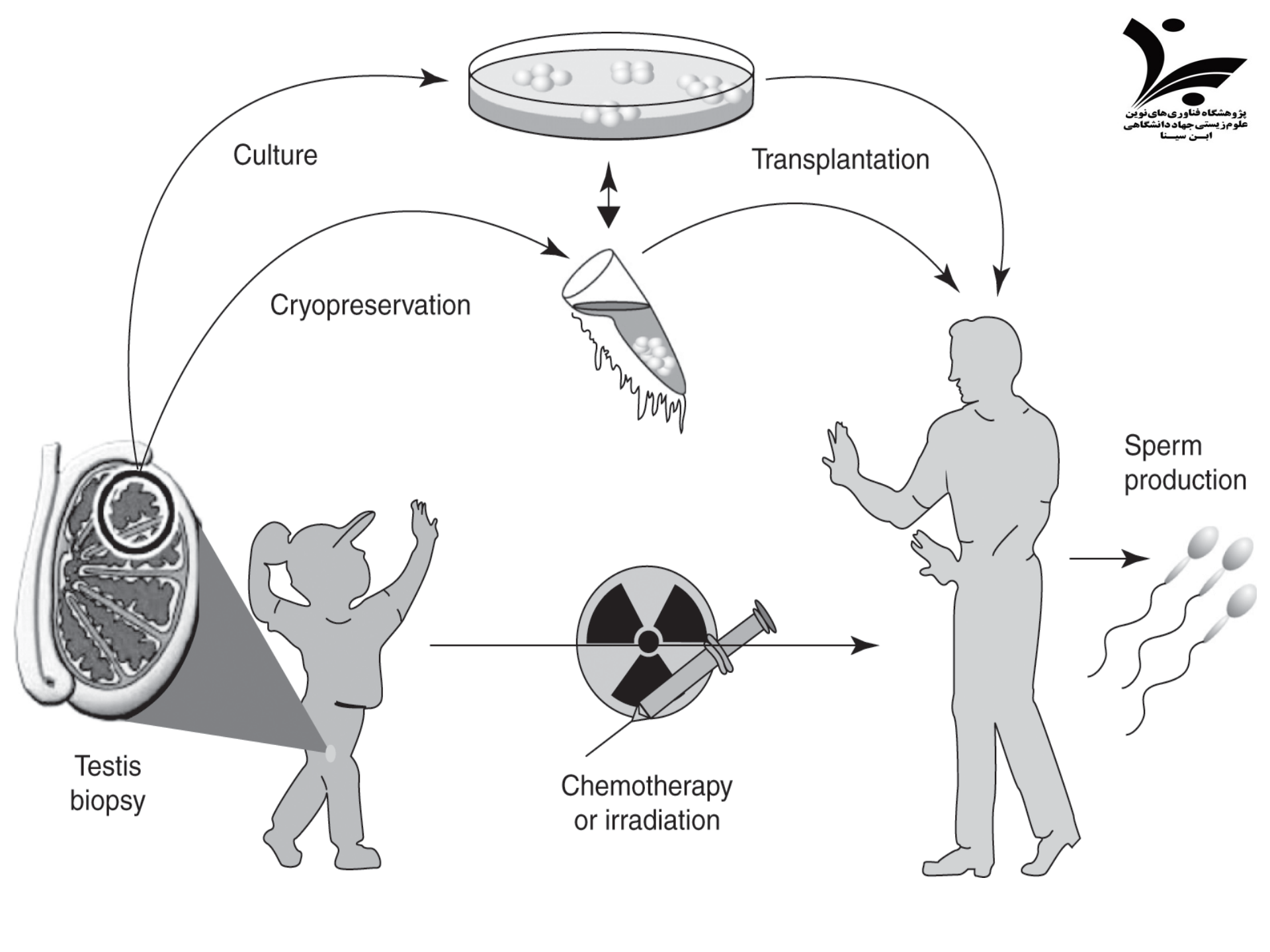
Children with Cancer

* Childhood cancers include *hematologic malignant conditions, sarcomas, central nervous system damages, leukemia, renal cancer, and bone cancer*

* Treatment with chemotherapy and radiation may also be necessary that these treatments can alter the function of the hypothalamic–pituitary–gonadal axis, as well as cause the testes are particularly vulnerable because germ cell can be severely damaged permanently affecting spermatogenesis

* prepubertal, no mature sperm is available for cryopreservation, and testicular tissue harvesting and cryopreservation are performed only in the context of experimental protocols

* At the present time, no proven methods of transforming the immature germ cells into mature, functional sperm exist, although this are currently under investigation


Culture
Transplantation
Cryopreservation
Sperm
production
Testis
biopsy
Chemotherapy
or irradiation

Fertility preservation options in female

* Female fertility is at risk following surgery, chemotherapy or radiotherapy

* Ovarian damage from drugs is *type and dose dependent* and is related to the patients' *age at the time of the treatment*, while the progressively smaller doses can also cause ovarian failure as the patients' age

* **Strategy for fertility preservation**:

  - Oocyte cryopreservation
  - Embryo cryopreservation
  - Ovarian tissue cryopreservation (OTC)
  - In vitro maturation (IVM)

Oocyte & Embryo cryopreservation

Mature oocyte is another strategy for fertility preservation in postpubertal females

* This process also requires ovarian stimulation and egg retrieval, for younger patients, oocyte storage is an option and the oocytes can be harvested if required by laparoscopy

* For postpubertal females storage is the best option for an adult woman who is married or in a stable relationship

* The limitations would include :

  - The paucity of time that there is between the detection of the cancer and the start of the treatment
  - The fact that only a limited number of embryos would be available for transfer at a later date

Ovarian Tissue Cryopreservation

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* At the moment, it is the only feasible option for prepubertal girls and the patients who must immediately start their chemotherapy or radiation treatment with inevitable delay

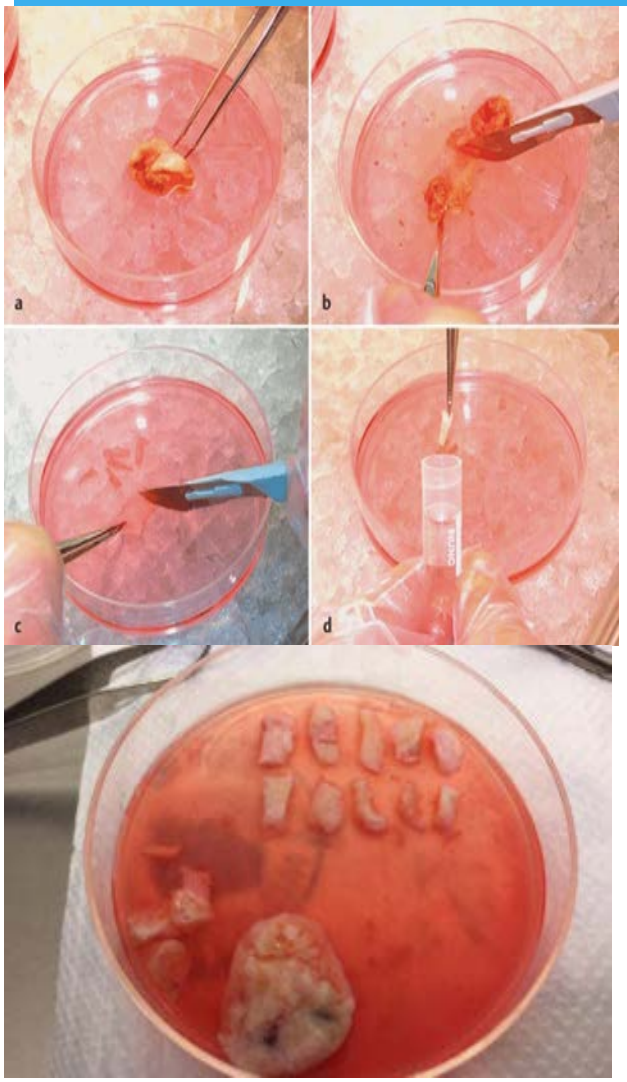
* Ovarian tissue banking is an acceptable fertility preservation technique and is the only method to preserve fertility for young adults, adolescent children & prepubertal girls since ovarian stimulation and IVF are not options

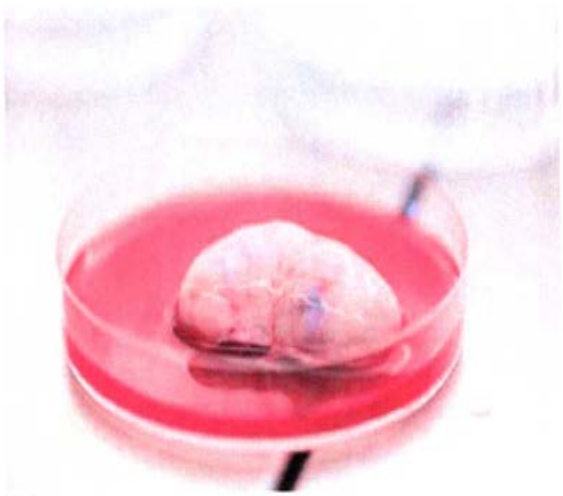
* Cryopreservation of ovarian cortical tissue theoretically represents an efficient way of preserving thousands of ovarian follicles at one time. This technique has been proposed principally for prepubertal females and for those who cannot delay cancer treatment in order to undergo ovarian stimulation and oocyte retrieval

* Laparoscopy is required to undertake a biopsy of an ovary or to remove the whole ovary for preservation

* The cortical tissue of the removed ovary contains the maximal number of ovarian follicles which can be pared off the medullary stromal tissue

Ovarian Cryopreservation

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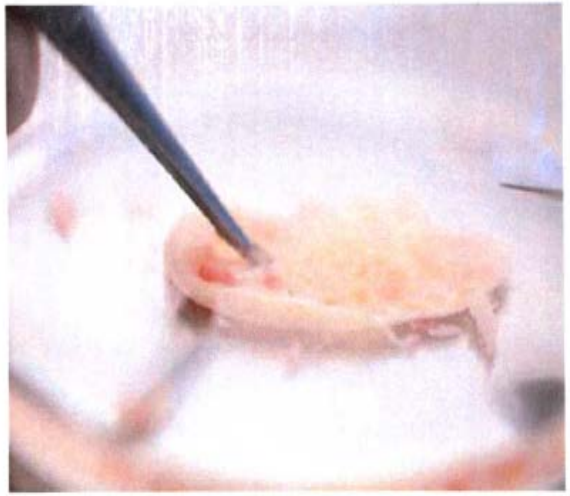
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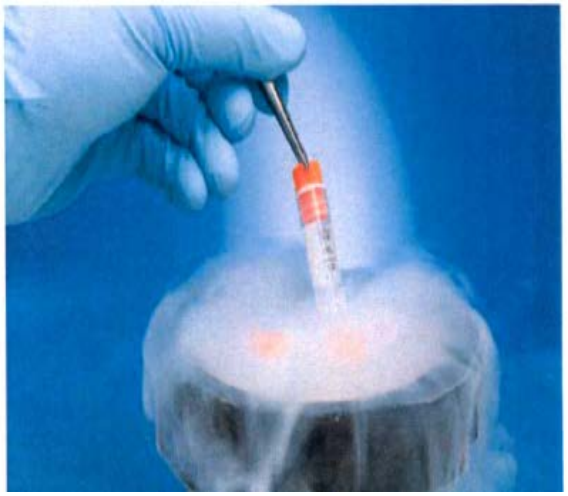
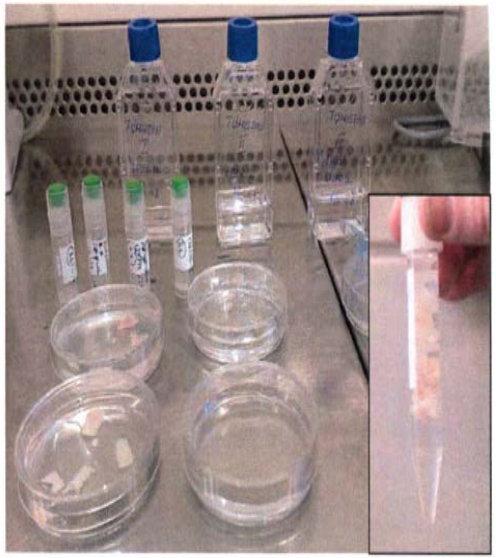
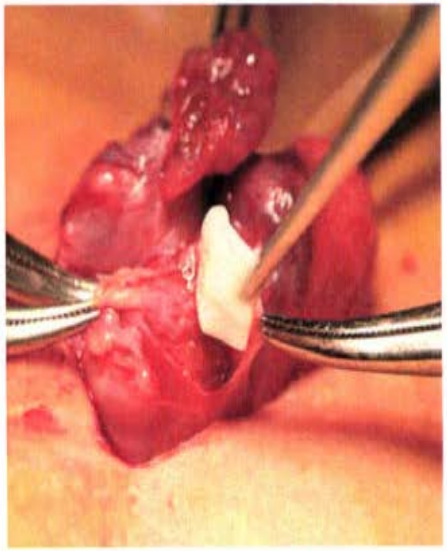
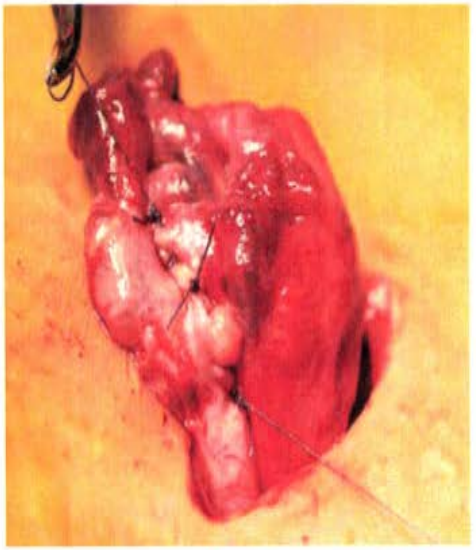
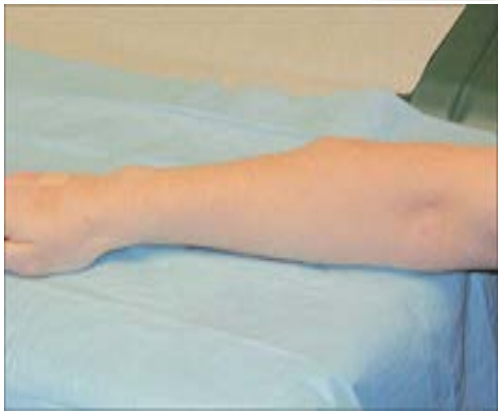


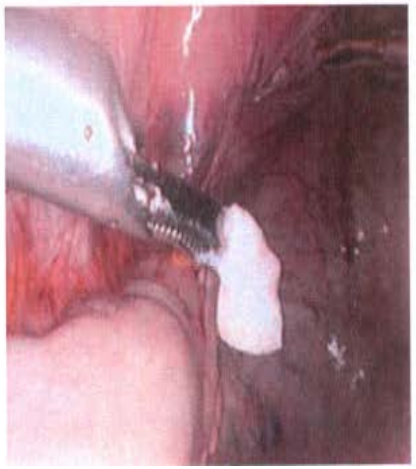
Ovarian transplant

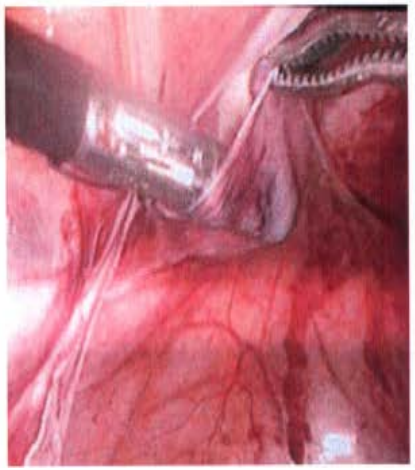


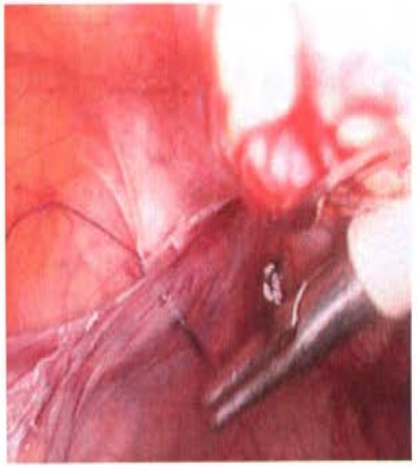


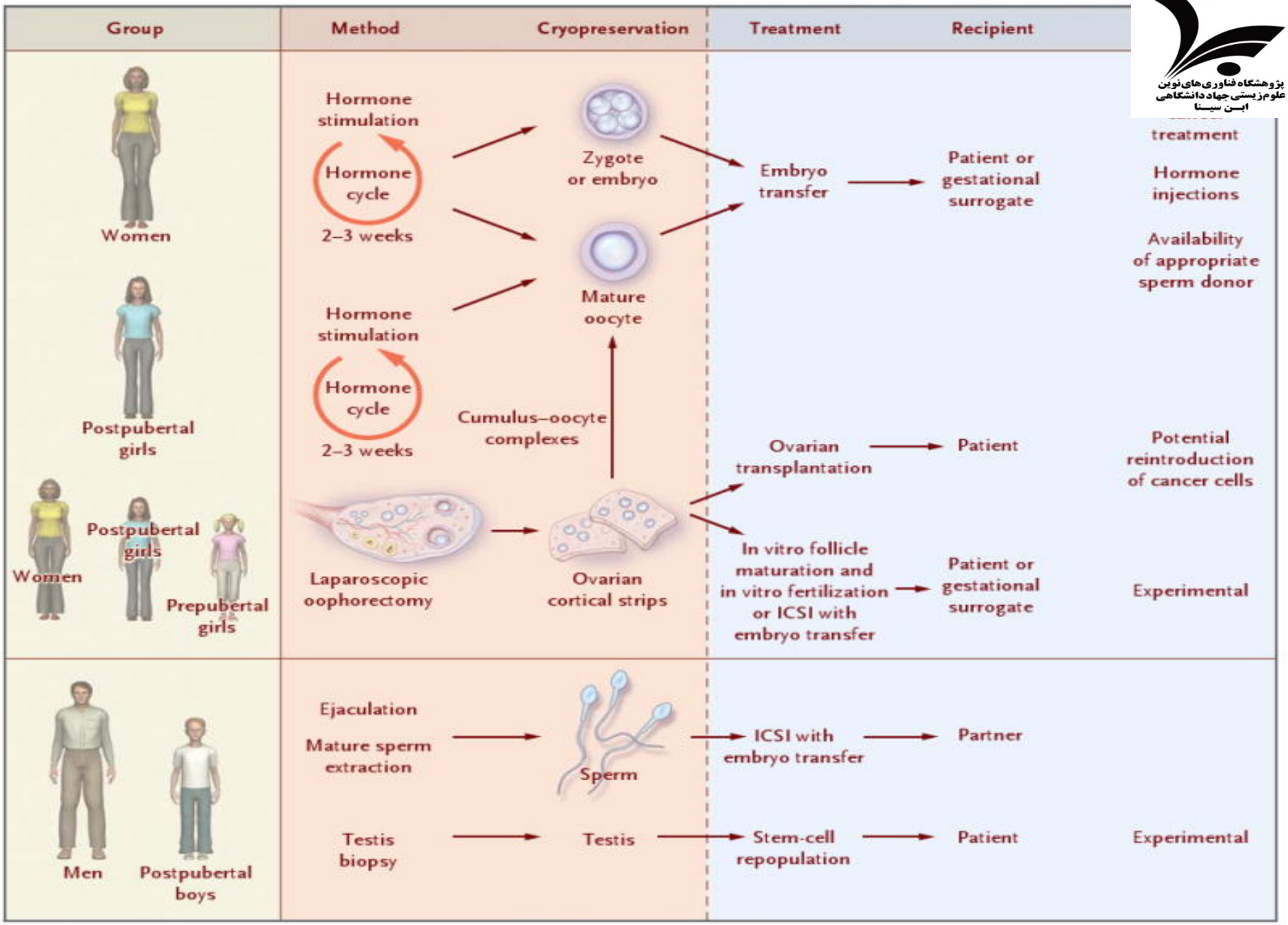












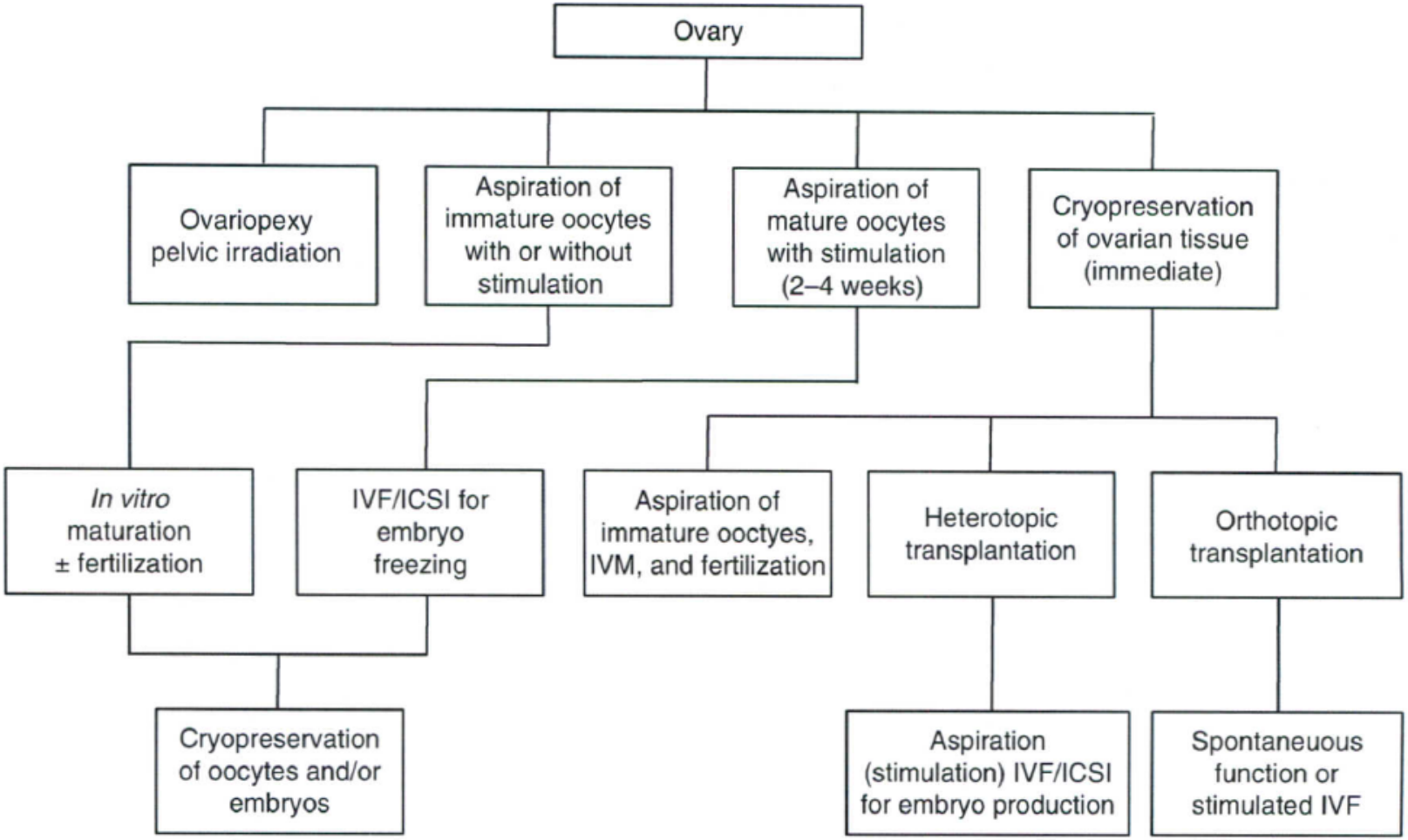
Barriers to Fertility Preservation

* The Society of Clinical Oncology has recommended that oncologists the possibility of infertility with reproductive-age cancer patients and involvement of male reproductive specialists should before fertility preservation consultation

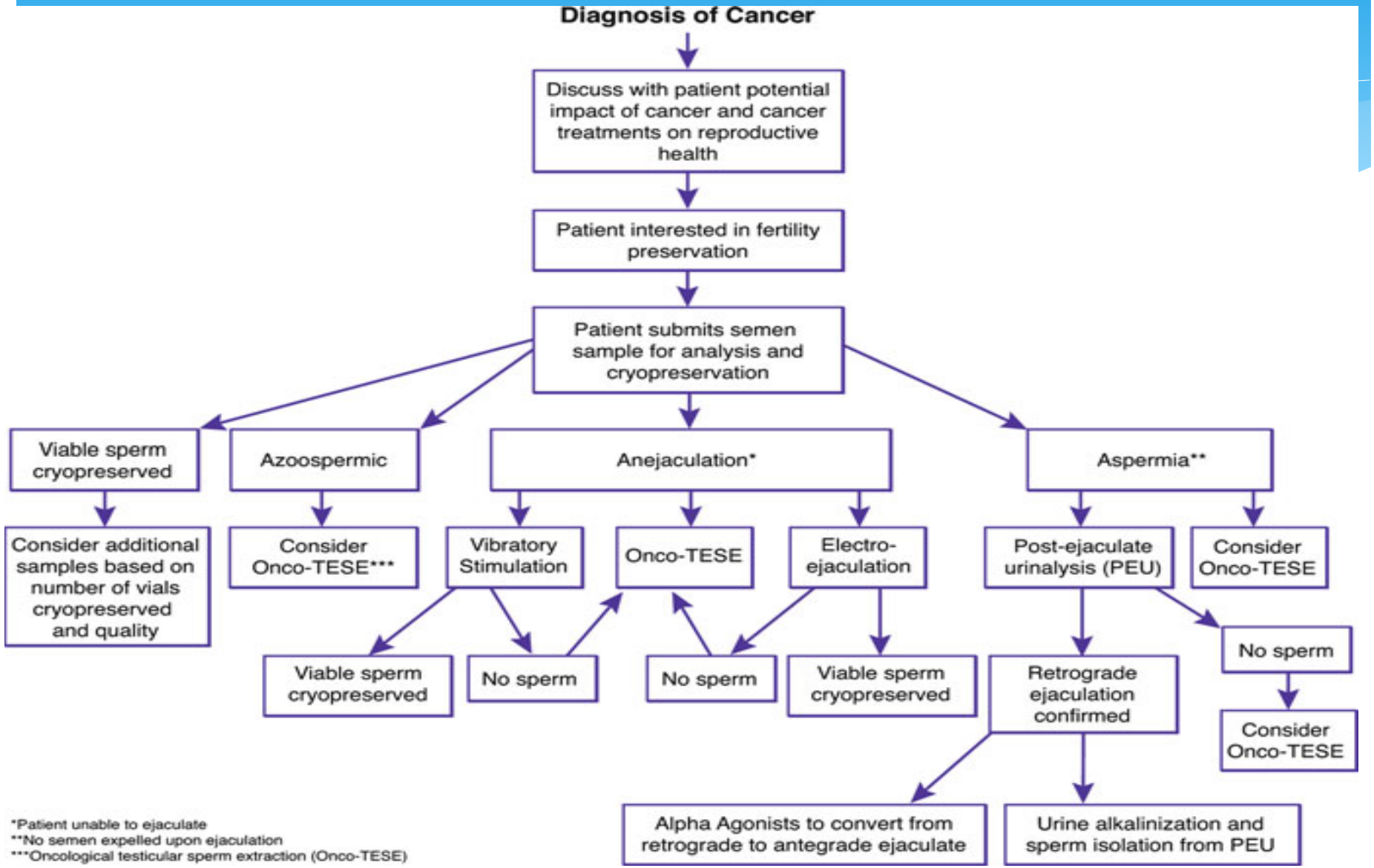
* Oncologists report several common barriers to the routine implementation of fertility preservation practices:
  - Desire to avoid delays in cancer treatment
  - Concerns about costs associated with fertility preservation
  - Other obstacles include a lack of adequate facilities
  - Lack of oncologist knowledge of preservation techniques
  - Lack of time to discuss the topic

Thank you for your attention

Ovary Cryopreservation



Male fertility preservation decision tree



* SUMMARY
* Patients facing treatments likely to impair reproductive function deserve prompt counseling regarding theiroptions for fertility preservation and rapid referral to an appropriate program.
* Embryo, oocyte, and ejaculated or testicular sperm cryopreservation remain the principle established modalities for fertility preservation.
* Ovarian tissue cryopreservation is no longer considered experimental and can be used in prepubertal patients or when there is not time for ovarian stimulation.
* Testicular tissue cryopreservation in prepubertal males is still considered experimental and should be conducted under research protocols when no other options are feasible.
* GnRH agonists can be offered to women with breast cancer and potentially other cancers for the purpose of protection from ovarian insufficiency. However, GnRH analogs should not replace oocyte or embryo cryopreservation as the established modalities for fertility preservation.
* GnRH agonist therapy is not effective in preserving fertility in men and is not recommended.
* Ovarian transposition may be offered to women undergoing pelvic radiation.