
مركز الخالدي الطبي

FERTILITY PRESERVATION AFTER CANCER TREATMENT

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Introduction

- Increase incidence of cancer during the reproductive age.
- Survival and cure rates of cancer are improving.
- One in 1000 adults is a survivor of childhood cancer.
- Better attention has been paid to prevention of reproductive failure.
- Increasing demand for fertility preserving interventions.

Distribution of cancers among women in the reproductive age.

Variable	Number/percent/ratio	Source
Female cancer cases in 2003	650,000	Jemal et al 2003
Percentage of cancers below the age of 40 ys	8%	Oktay and Yih 2002
Survivors of all childhood cancers	270,000(1/1000 population)	Simon 2003
Survivors of all childhood cancers in 2010	1/250 patients	Bleyer 1990

CONSEQUENCES OF MULTI-AGENT CHEMOTHERAPY AND HIGH DOSE RADIOTHERAPY

- Premature ovarian failure (POF).
- Early pregnancy loss.
- Premature labour.
- Low birth weight.

Reproductive age malignancies treated with chemotherapy.

- ALL; acute lymphoblastic leukemia.
- Hodgkin's Lymphoma.
- Neuroblastoma.
- Non-Hodgkin's Lymphoma.
- Wilm's tumor.
- Ewing's sarcoma.
- Genital rhabdomyosarcoma.

BREAST CANCER

- The commonest malignancy in women during reproductive age.
- One out of every 228 women will develop breast cancer befor 40 years of age.
- 15% of all breast cancer occur at <40 years.

CANCER CERVIX

- 13.000 new cervical cancer were diagnosed in USA.
- 50% of the new cases < 35 years of age.

Autoimmune diseases treated with chemotherapy.

- SLE; systemic lupus erythematosus (incidence 3 per 1000 people)
- Behcet's disease.
- Autoimmune glomerulonephritis.
- Crhon's disease.
- Ulcerative colitis.
- Pemphigus vulgaris.

HAEMATOPOIETIC STEM CELL TRANSPLANTATION (HSCT)

Pre-existing bone marrow ablation using cytotoxic chemotherapy is a pre-requisit before HSCT.

Factors affecting the extent of chemotherapy induced gonadotoxicity.

- Type, duration, dose.
- Gonatotoxicity induced by chemotherapy is almost irreversible.

  (● decreased number of follicles to absent follicles)

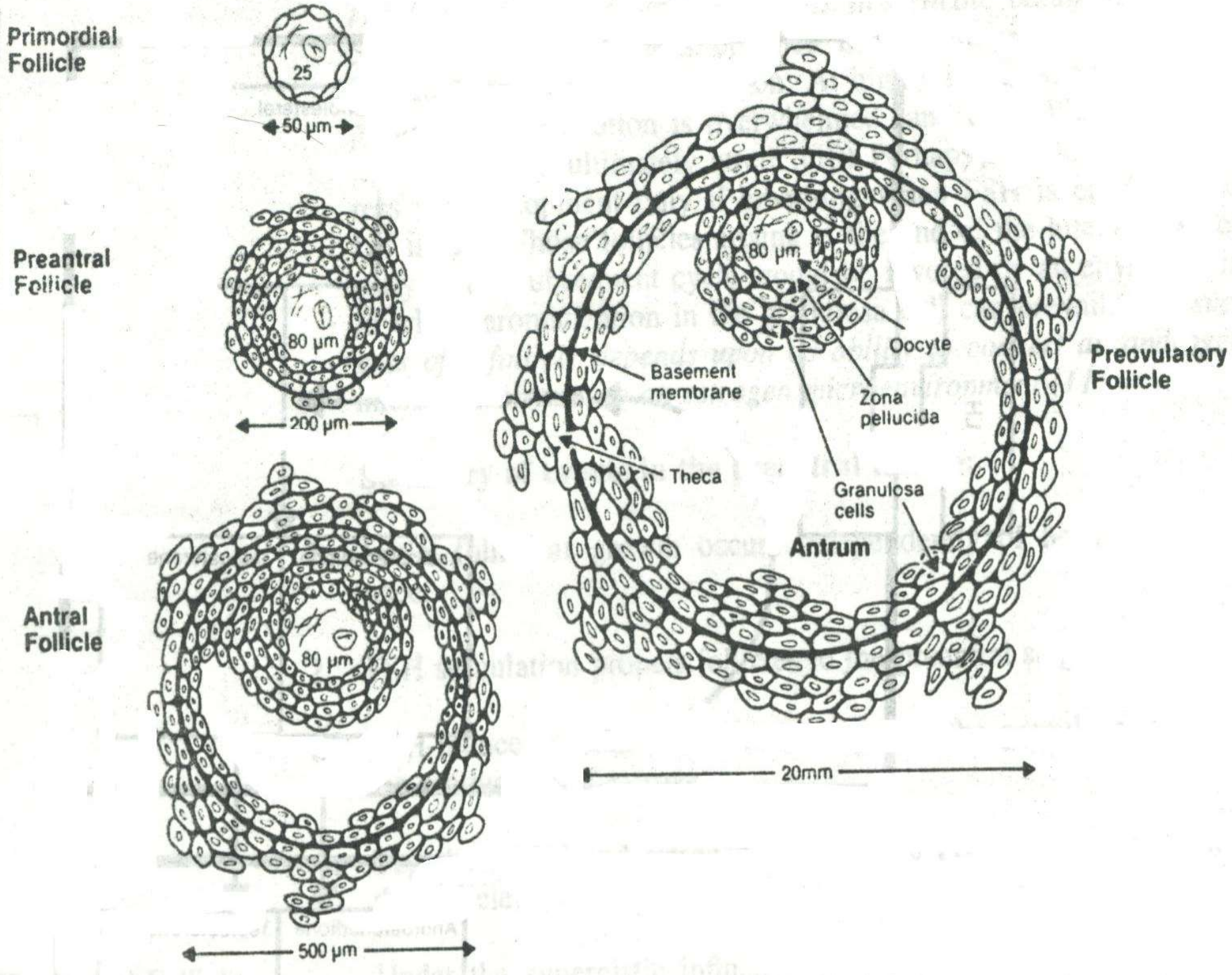
  (● fibrosis)
- Amenorrhea ranges 0-100 %
  - younger age group 21 -71%
  - older age group 49 - 100%
- The risk of gonadal damage increases with age (lower number of oocytes).
- Temporary amenorrhea or permanent.

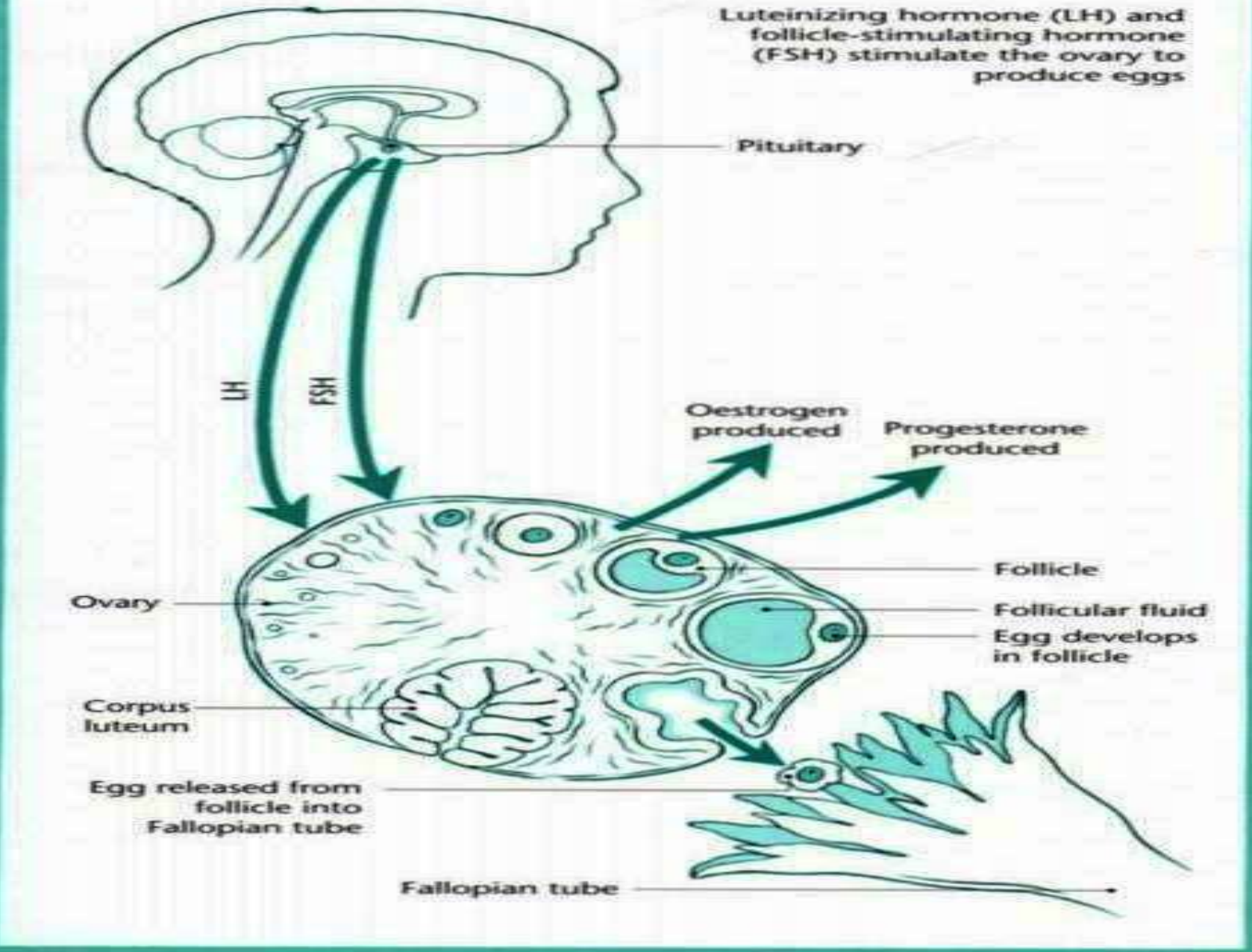
Effect of different chemotherapeutic agents on the ovarian functions

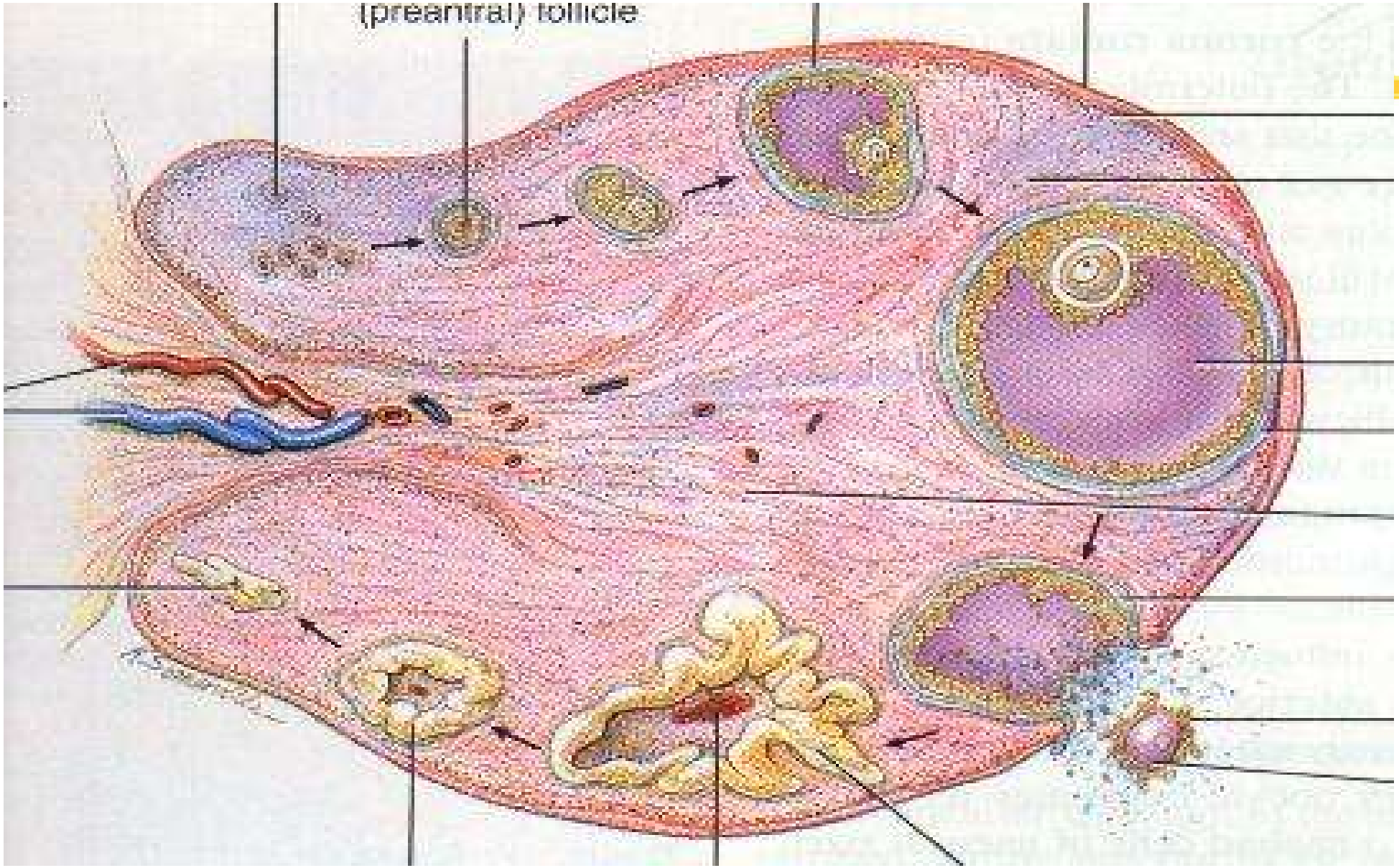
	Cell Cycle Phase-Specific Agents			
Drug type	**G1 Phase**	**S Phase**	**G2Phase**	**M Phase**
Individual drugs	**L-asparaginase, Prednisone**	**Cytrabine, fluorouracil, hydroxyurea, methotrexate, thioguanine**	**5-Bleomyosin etoposide**	**Vinblastine, vincristine, vindesine, Paclitaxel**
Extent of ovarian Damage	**No/low risk**	**No/low risk**	**No/low risk**	**No/low risk**

Effect of different chemotherapeutic agents on the ovarian functions

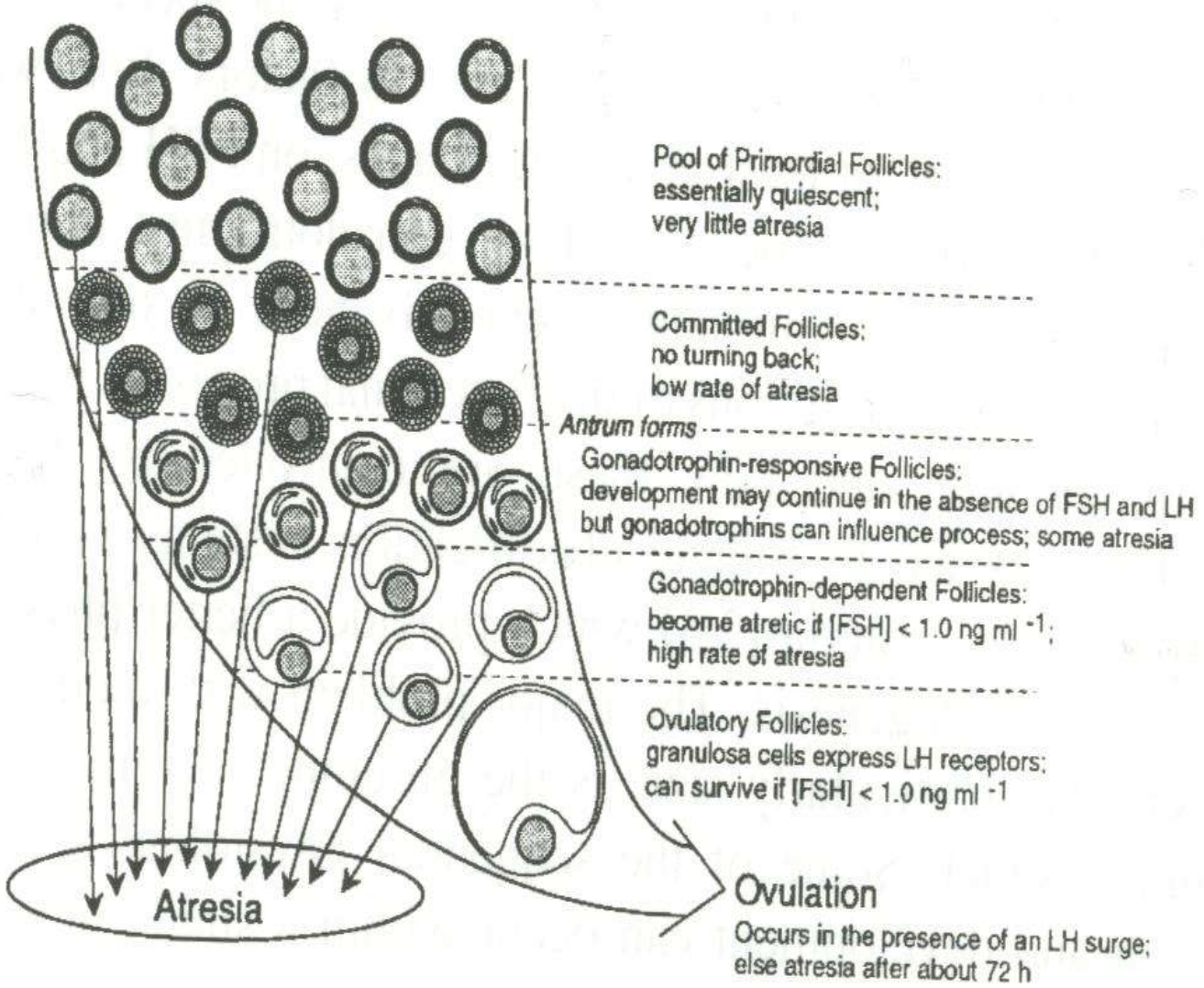
	Cell Cycle Phase-NonSpecific Agents			
Drug type	Alkylators	Antitumor Antibiotics	Nitrosureas	Miscellaneous
Individual drugs	Busulfan, carboplatin, chlorambusil, cisplatin, cyclophosphamide isofamide, mechlorethamine, melphalan	Dactinomycin, daunorubicin, doxorubicin, mitomycin, mitoxantrone	Carmustine, lomustine, streptozocin	Dacarbazine, procarbazine
Extent of ovarian damage	High	Intermediate	Intermediate	High

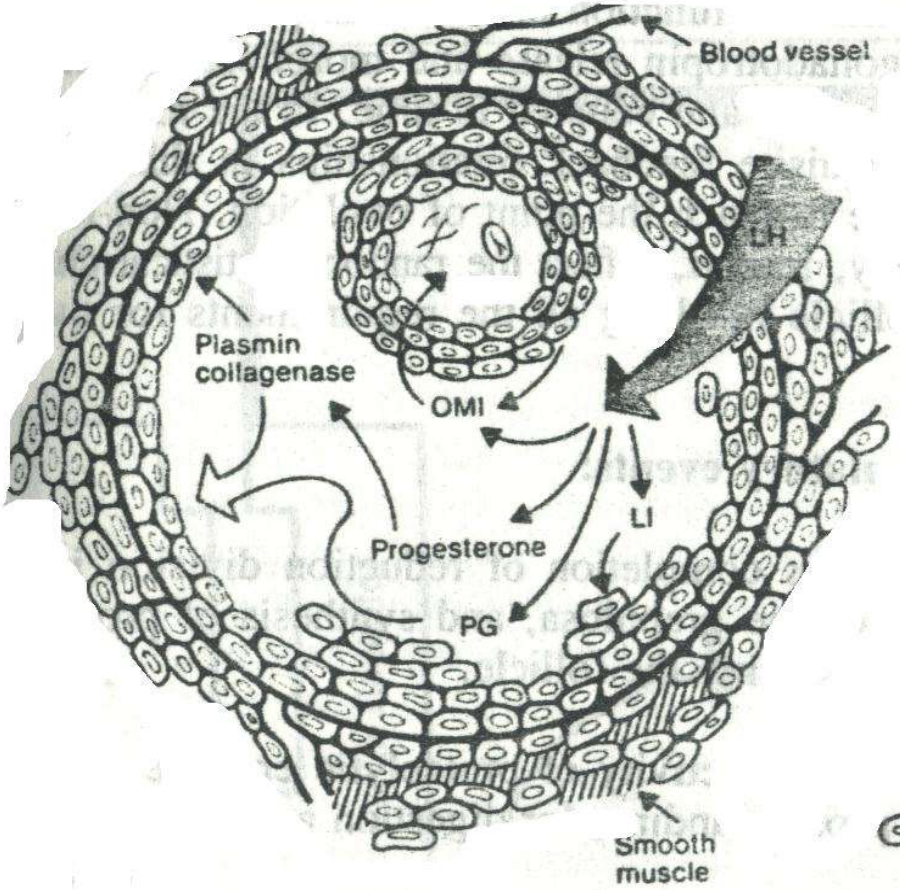

Primordial Follicle
25
50 µm
Preantral Follicle
80 µm
200 µm
Antral Follicle
80 µm
500 µm
80 µm
Oocyte
Basement membrane
Zona pellucida
Theca
Granulosa cells
Antrum
Preovulatory Follicle
20mm

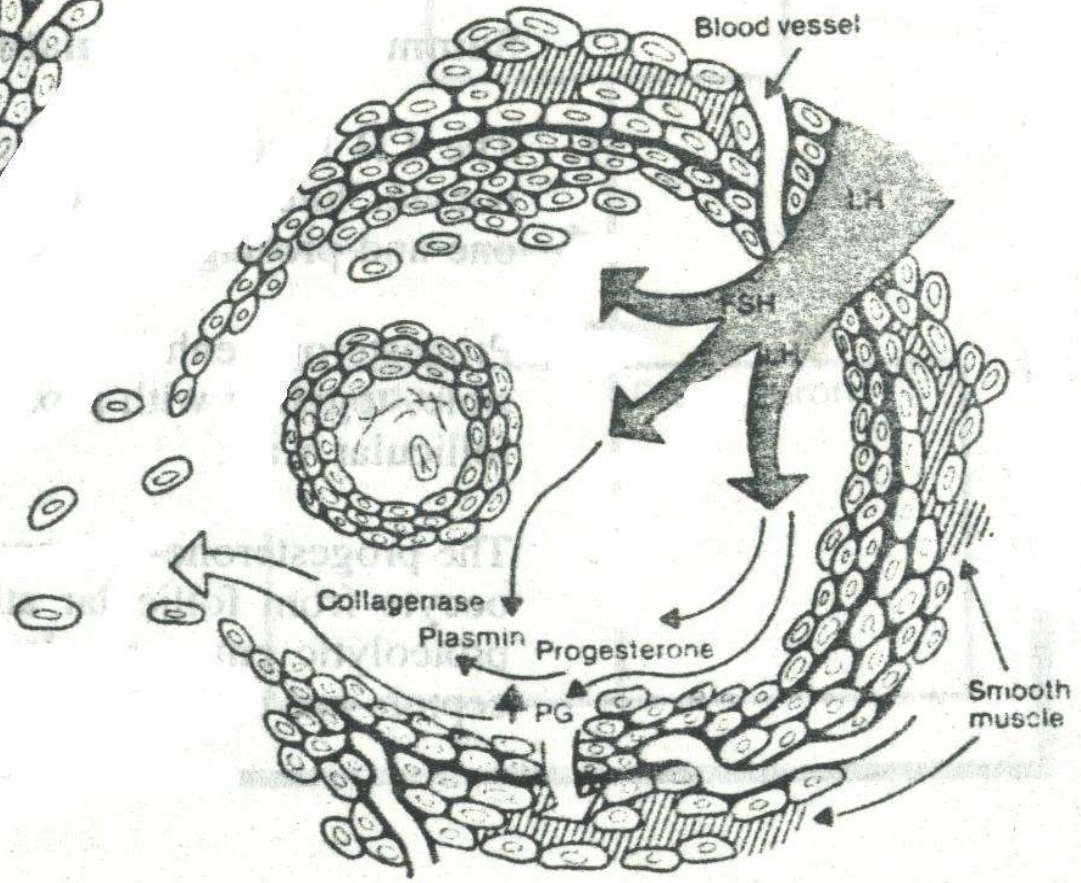



(preantral) follicle

Ovulation


Pool of Primordial Follicles:
essentially quiescent;
very little atresia
Committed Follicles:
no turning back;
low rate of atresia
Antrum forms
Gonadotrophin-responsive Follicles:
development may continue in the absence of FSH and LH
but gonadotrophins can influence process; some atresia
Gonadotrophin-dependent Follicles:
become atretic if [FSH] < 1.0 ng ml -1;
high rate of atresia
Ovulatory Follicles:
granulosa cells express LH receptors;
can survive if [FSH] < 1.0 ng ml -1
Atresia
Ovulation
Occurs in the presence of an LH surge;
else atresia after about 72 h


Blood vessel
LH
Plasmin
collagenase
OMI
LI
Progesterone
PG
Smooth
muscle


Blood vessel
LH
SH
LH
Collagenase
Plasmin
Progesterone
PG
Smooth
muscle

Differential sensitivity of different cellular components of the ovary

- Impaire follicular maturation.
- Deplete primordial follicles.

Dose of chemotherapy

- Cumulative dose of the cytotoxic drug
- Younger women require higher cumulative doses.
- The average dose
  - 40 years 5200 mg.
  - 30 years 9300 mg.
  - 20 years 20.400 mg
- Older women have a shorter duration of onset of amenorrhea

<40years 6-16 months.

>40years 2-4 months.

Regimen used in Breast Cancer and POF

* CME 60% (2/3) will become amenorrhoic.
* AC (doxorubicin, cyclophosphamide).
  34% will be amenorrhoic at 3 years.
* Taxanes are worse.

*CME: (cyclophosphamide , methotrexate , 5 fluoro-uracil).

Radiotherapy induced ovarian failure

Cancers include: - cervical.
- vaginal
- ano-rectal carcinomas.
- some germ cell tumors.
- CNS tumors.
- 50% of the patient with ca. cervix are premenopausal.
- 1/3 under 40 years of age.

Effect of radiation dose and age on ovarian function

Ovarian dose (cGy)	Risk of ovarian failure
60	No deleterious effect
150	No deleterious effect in young women ; some risk for sterilization in women older than 40
250-500	In women aged 15-40, 60% permanently sterilized; remainder may suffer temporary amenorrhea. In women older than 40, 100% permanently sterilized
500-800	In women aged 15-40, 60%-70% permanently sterilized; remainder may experience temporary amenorrhea. No data available for women over 40 .
>800	100% permanently sterilized

Factors affecting the extent of radiotherapy induced gonadotoxicity

- 1. Patient's age.
- 2. Dose of radiation (Breaking point 300cGy).
- 3. Extent.
- 4. Type of radiation (abdominal, pelvic external beam, brachytherapy).
- 5. Fractionation of the total dose.

Break point for radiation is around 300cGy

- 11-13% had POF <300cGy.
- 60-63% had POF >300cGy.
- >6Gy → irreversible ovarian failure.
- < 2Gy → 50% of the oocyte population is destroyed. (LD5O<2Gy).

Long-term reproductive functions after radiotherapy

- Ovaries in the irradiation field; POF 68%
- At the edge field; POF 14%.
- One ovary outside the field; No failure.

(Stillman RJ et al, Am J Obstet Gynecol)

Complication when pregnancy

- Early pregnancy loss “Abortions”.
- Premature labour.
- Low birth weight.

Fertility Preservation Strategies

- Pharamacolgical protection.
- Ovarian transposition.
- Oocyte cryopreservation.
- IVF and cryopreservaion of preimplantation embryos.
- Cyropreservation and transplantation of ovarian tissue.

Pharmacolgic protection

- A) GnRH agonists.
  - Premenarchal gonads appear to be least sensitive to cytotoxic drugs.
  - By suppressing gonadotrophin.
  - No protection effect of radiation therapy.
  - No protetive effect on male gonads.
- B) Apoptotic inhibitors.

  (Sphingosine – 1- phosphate)

  apoptosis could be activated by chemotherapeutic drugs.

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.

Reproductive function of transposed ovaries.

- 89% spontaneous pregnancy with 75% occurring without repositioning.
- repositioning is done in cases of infertility.
- 11% conceived with IVF.

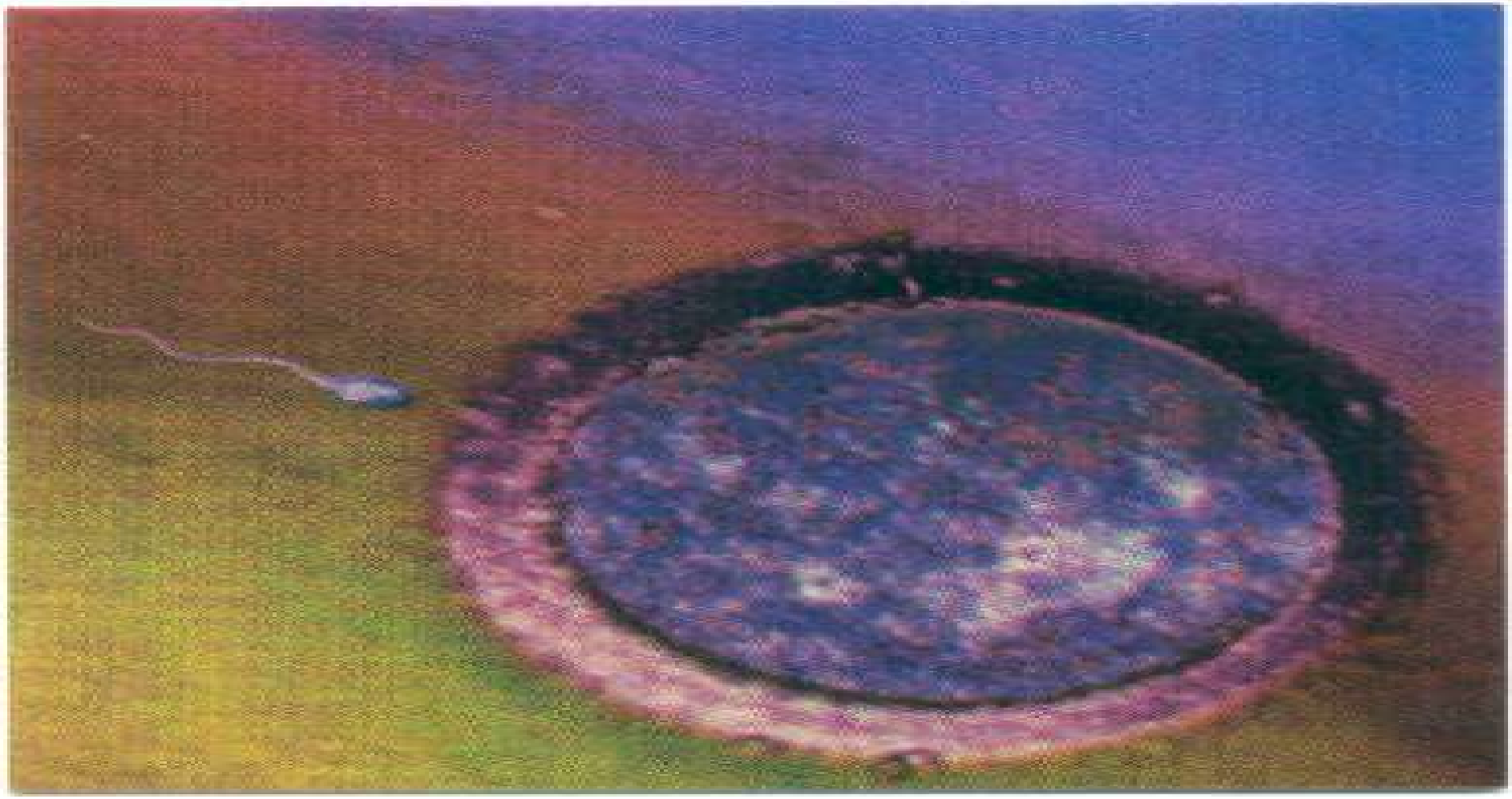
Reproductive function of transposed ovaries.

- Controversies regarding pregnancy outcomes after pelvic irradiation.
  - ? Increase fetal wastage
  - ? Birth defects
  - ? Low birth weight
  - ? Abnormal karyotype
  - ? Cancer in the offspring
  - ? Spontaneous abortions

- advice: delay pregnancy for a year after completing radiation therapy.

Complications of oophropexy

- Fallopian tube infarction.
- Chronic ovarian pain.
- Ovarian cyst formation.
- Migration of ovaries back to their original position.
- Ovarian metastasis (No increased risk).

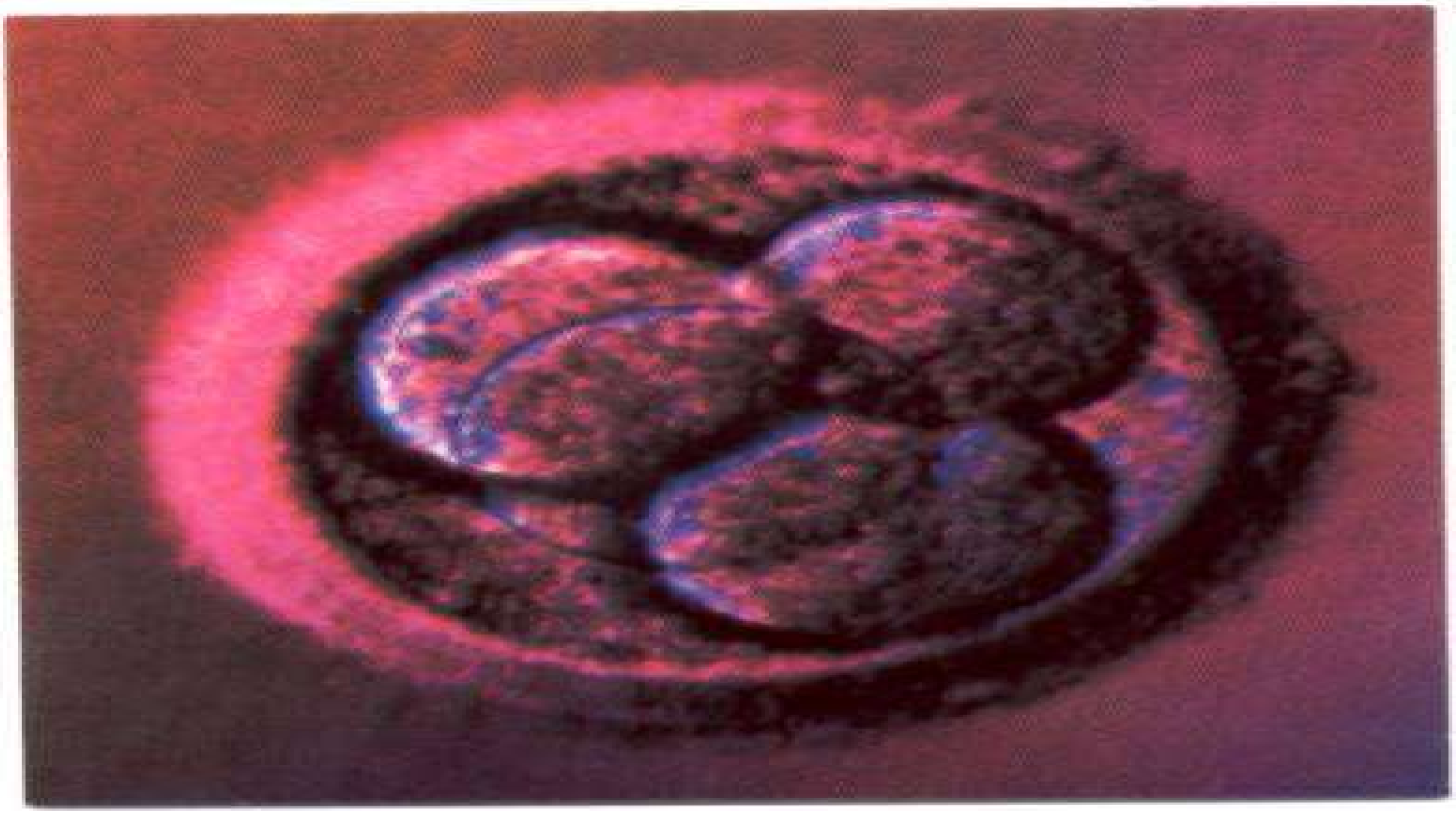


Oocyte Cryopreservation.

- for single women, ethically accepted.
- Oocytes are more sensitive to freezing–thawing procedures than embryos.
- Results are still very low.
- Alternative strategy is to freeze immature oocytes (primordial follicle).
- Other alternative is vitrification; survival rates are 68.4%6 & 48.5%.

Cryopreservation of preimplantation embryos

- 18.6% success rates.
- Survival rates of embryos between 35 and 90%.
- 8 – 30% implantation rates.
- Not acceptable to prepubertal, adolescent and women without a partner.



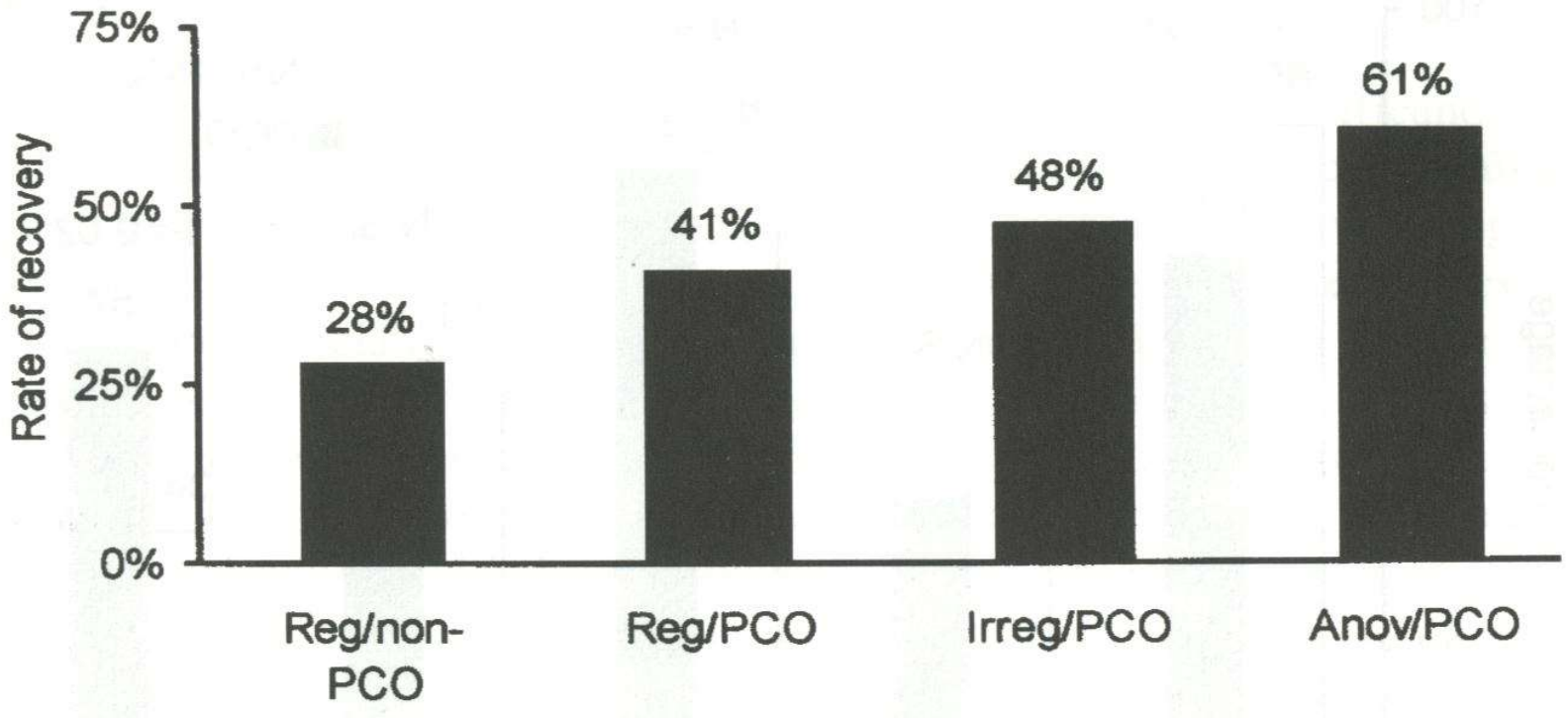
Ovarian stimulation protocols in estrogen–sensitive cancers.

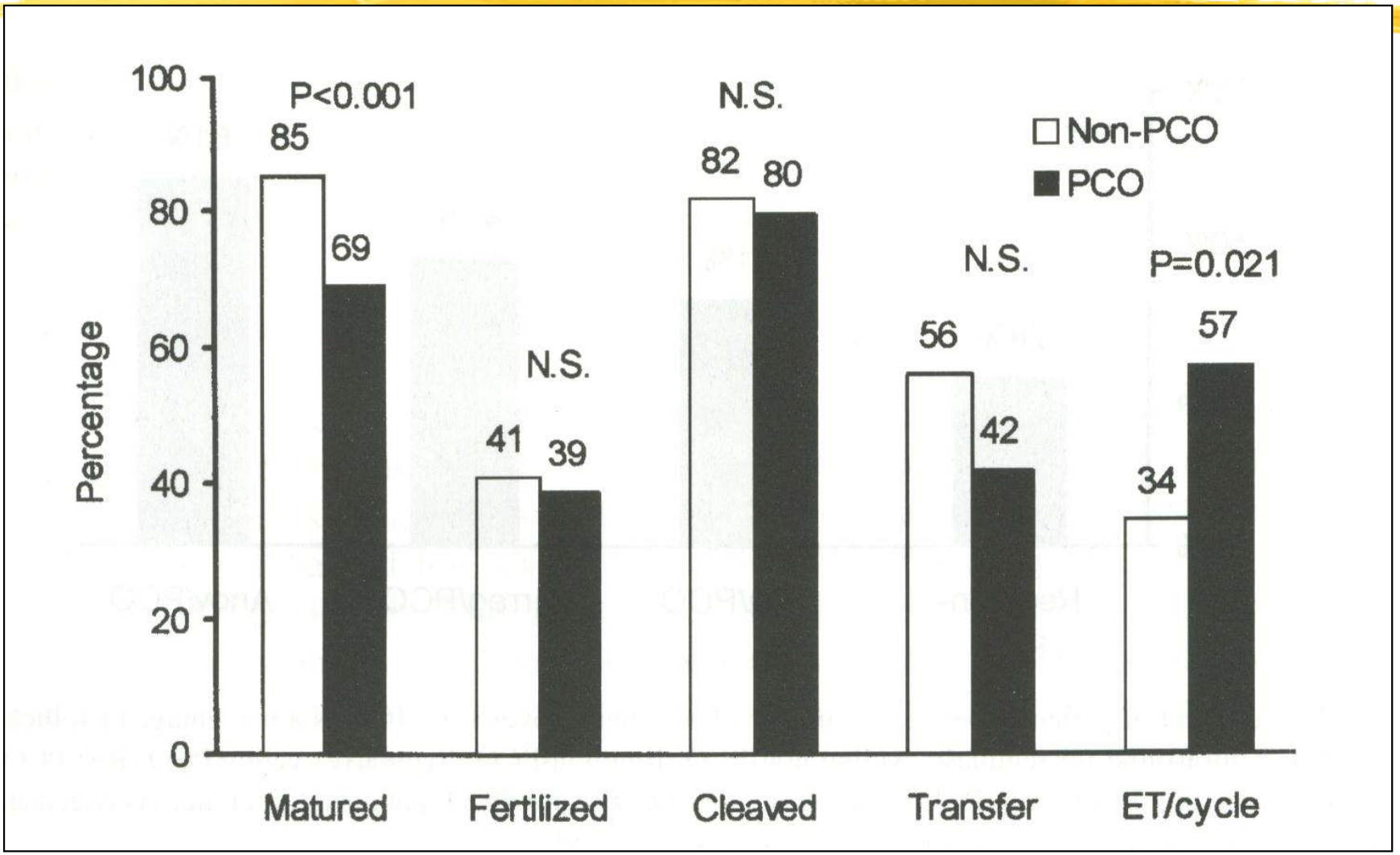
- Short flare – up protocol.
- Natural cycle IVF.
- Tamoxifen (Anti–estrogen)
- Letrozole suppresses plasma ostradiol, estrone and estrone sulphate levels.

In vitro oocyte development (IVM)

- Harvesting immature follicles (they may become atretic).
- More oocytes became available for clinical treatment.
- No large doses of gonadotropic hormones for stimulation.
- IVG In Vitro Growth of very small follicles (primordial or prenatal follicles).

Percentage of oocyte recovery from follicles, effect of patient type.




100
80
60
40
20
0
Percentage
P<0.001
N.S.
N.S.
P=0.021
85
69
41
39
82
80
56
42
34
57
Non-PCO
PCO
Matured
Fertilized
Cleaved
Transfer
ET/cycle

Studies and results about IVF outcome from IVM oocytes

- Goud P.T and his colleagues studied the role of cumulus cells and EGF in the culture media. They concluded that: EGF- supplemented media of the cumulus-intact oocytes during culture improve nuclear and cytoplasmic maturation.

Ovarian stimulation protocols in non-estrogen sensitive cancers.

- IVF before cancer treatment and cropreservation.
- IVF after cancer treatment.

  (poorer responses)

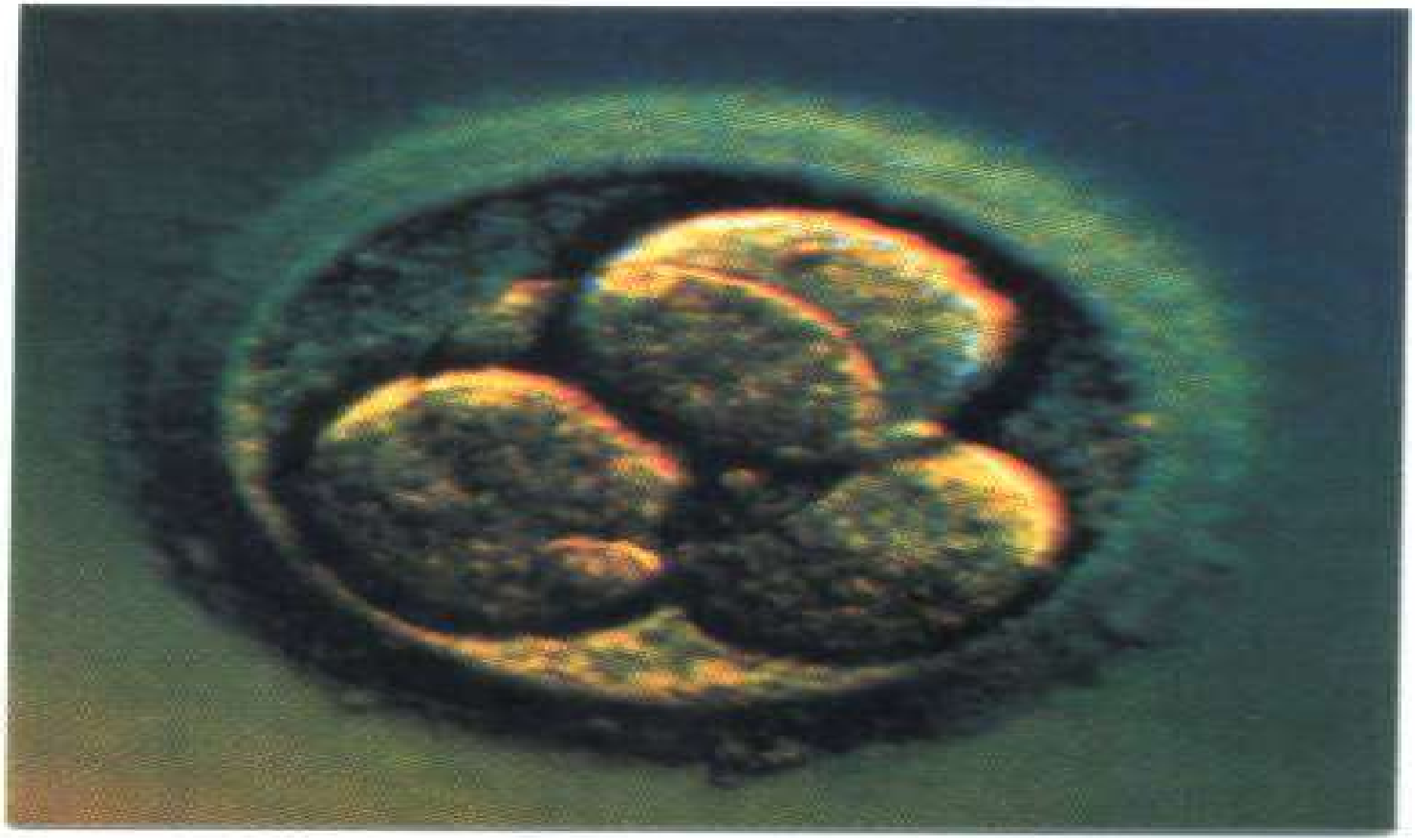
Cryopreservation and transplantation of ovarian tissue.

- Still experimental procedure.
- Limited studies.
- Primordial follicles should have better survival rates.
- In vitro – growth of primordial follicles.
- (after immune deficient animal host).

  trans–species viral infections.
- Transplanted back into patient,

  (Cancer nidus).

  after cryopreservation.



Autografting of human ovarian tissue

Ovarian cortical strips transplantation.

- in the pelvic wall.
- in the forarm.
- lower abdominal skin.

Xenogafting

mice (retroviral infections).

Ovarian cancer and Infertility / infertility treatment

Ovarian Cancer and Infertility

- Ovulation is associated with an increased risk of epithelial ovarian cancer. (epithelia proliferation, inclusion cyst formation).
- Oncogenes HER-2/meu
  K-ras
  c-myc
  mutations P53 tumor-suppressor gene.

Cancer and IVF

Cases exposed to IVF treatment 5 years follow-up

	0bserved After IVF	Suspected After IVF	Unexposed observed	Unexposed suspected
Breast	16	17.9	18	18.29
Ovarian	3	1.7	3	1.85
Uterus	2	0.9	3	0.86
Melanoma	7	7.36	9	7.55
Colorectal	1	2.75	3	2.66
Cervix	5	5.03	1	5.16
All cancers	42	44.51	48	44.24

Material risks with various events

Table 3 Material risks with various events and community activities

Activity	Chance of death in one year
Motor cycling	1 in 1000
Hysterectc	1 in 1600
Driving a car	1 in 6000
Power boating	1 in 6000
Rock climbing	1 in 7500
Continuing pregnancy	1 in 14 000
Playing football	1 in 25 000
Laparoscopy	1 in 67 000
Canoeing	1 in 100 000
Having sexual intercourse (PID)	1 in 100 000
RU486 use	1 in 200 000
Using tampons	1 in 300 000
Legal termination of pregnancy: <9 weeks	1 in 500 000
Jumbo jet flight	1 in 2 000 000

Conclusion.

- GnRH analogues are the only available medical protection for chemotherapy.
- Laparoscopic ovarian transposition is a good option if radiotherapy is to be used.
- Oocyte cryopreservation is gaining popularity.
- Embryo cryopreservation is the most successful fertility preservation.


THANK YOU