

Assisted Reproduction

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Semmelweis University**

Definition of Infertility

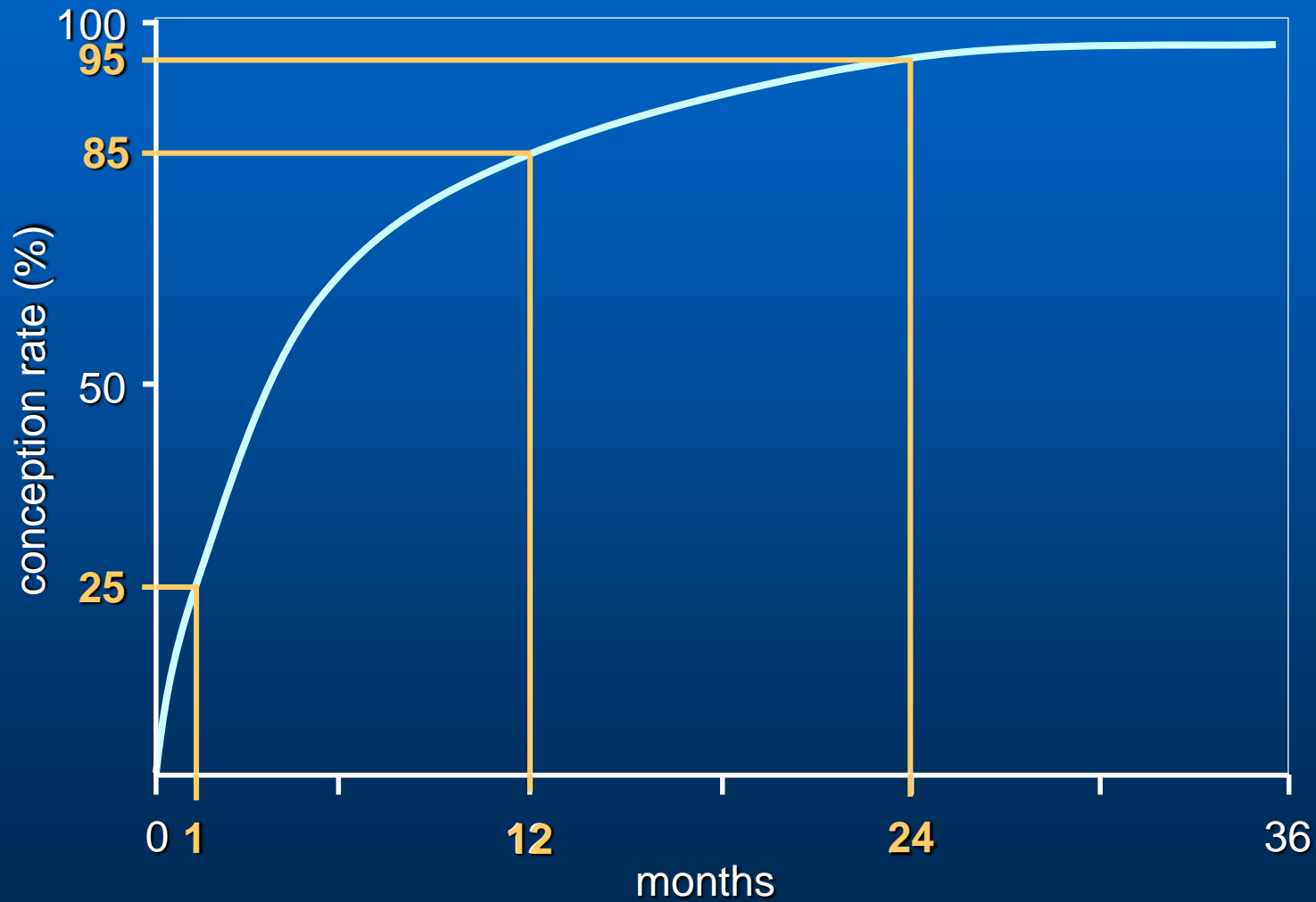
No conception inspite of

regular,

intercourse without any contraception

within one (two) year(s).

Natural Conception Rate



Prevalence of Infertility

Age (year)	Prevalence (%)
15-19	2,1
20-24	6,4
36-39	12,5
40-44	15,9

(Formosa and Brincat 1994)

Forms of Infertility

Primary

Secondary

Cause of Infertility

Female origin



Male origin



30%

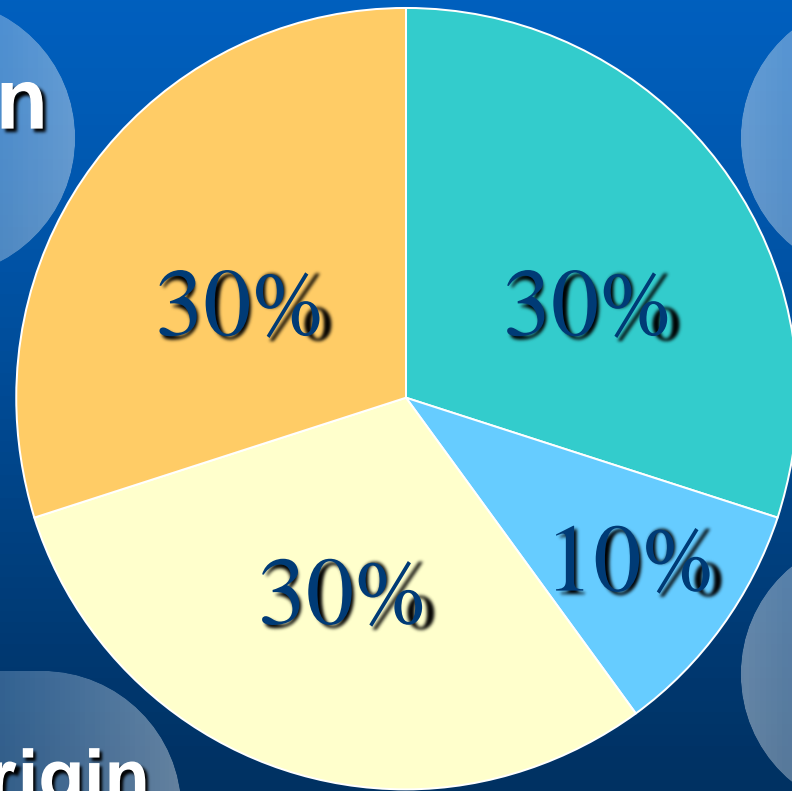
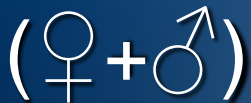
30%

30%

10%

Unknown origin

Female+male origin



Etiology of Female Infertility

Ovulatory	40 %
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Anatomical	50 %
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Psychic	10 %
---------	------

Female Infertility Caused by Ovulation Disorder

Central

Hypophysis (trauma, tumor, congenital)
Hypothalamus
Corpus Luteum Insufficiency (CLI)

Hyperprolactinaemia (functional, drug, tumor)
Polycystic Ovary syndrome (PCOS)

Peripheral

Gonadysgenesis (Turner-syndrome)
Premature Ovarian Failure (POF)

Ovarian Tumor
Resistant Ovary Syndrome

Metabolic

Thyroid Gland Diseases
Hepatic Diseases
Pathologic Obesity/Emaciation

Hyperandrogenic Disorders (adrenal gland, tumor)

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Metabolic

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Hepatic Diseases
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Hyperandrogenic Disorders (adrenal gland, tumor)

Female Infertility

Caused by Anatomic Disorder

Cervix

Müllerian-duct developmental anomalies
Cervical stenosis
Postoperative status
(cone biopsy, cryotherapy)

Cervicitis
Diethyl-stilbestrol (DES) exposure
Cervical mucus anomalies

Corpus

Malformation (Mayer-Rokitansky-Küster-Hauser syndrome)
Submucosus leiomyoma

Intrauterin adhesions
(Asherman-syndrome)

Fallopian tube

Pelvic Inflammatory Disease (PID)
Endometriosis

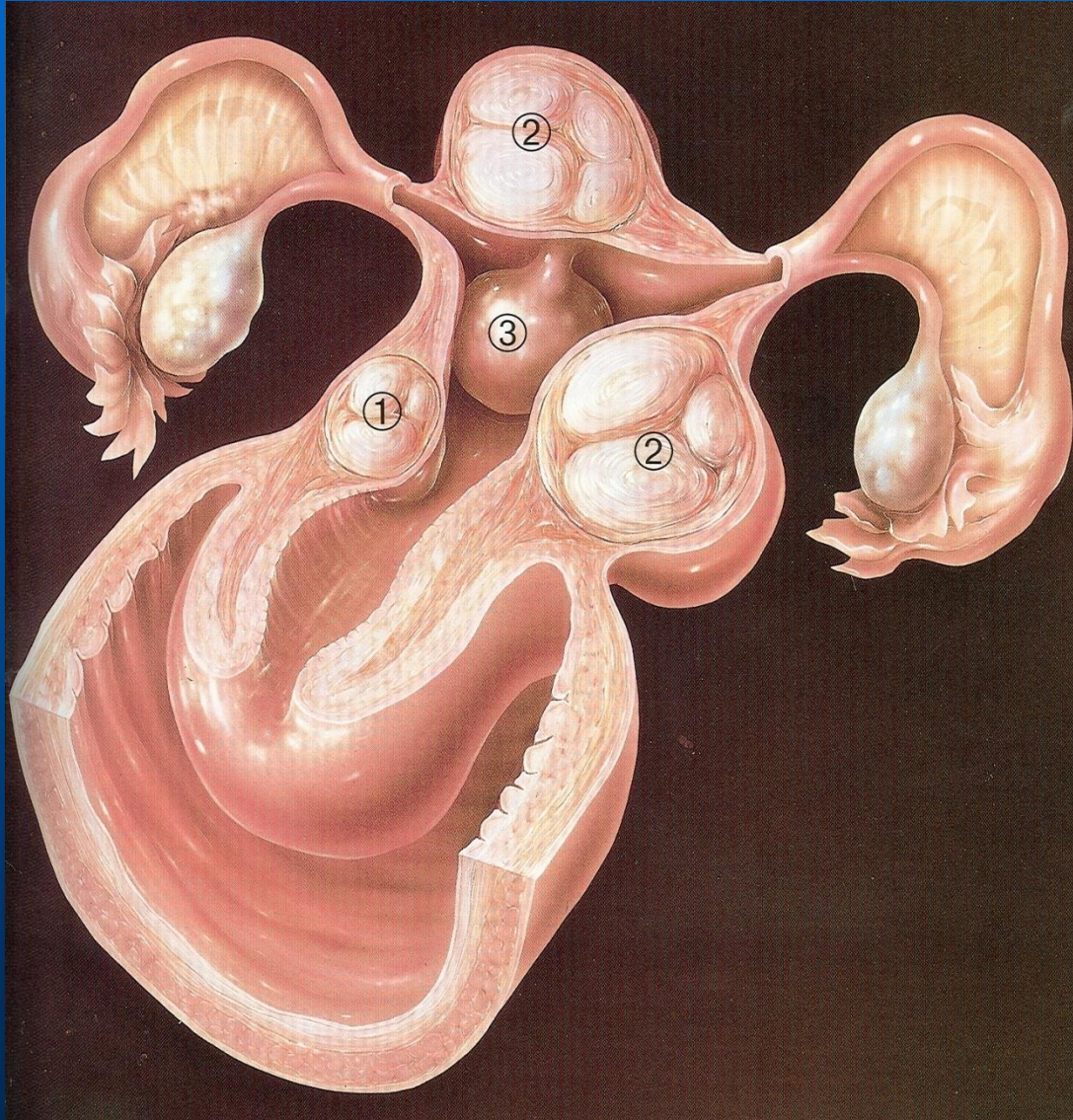
Post-sterilisation status

Peritoneal factor

Pelvic adhesions

Endometriosis

Myoma



Female Infertility

Cervix Caused by Anatomic Disorder

Müllerian-duct developmental anomalies
Cervical stenosis
Postoperative status
(cone biopsy, cryotherapy)

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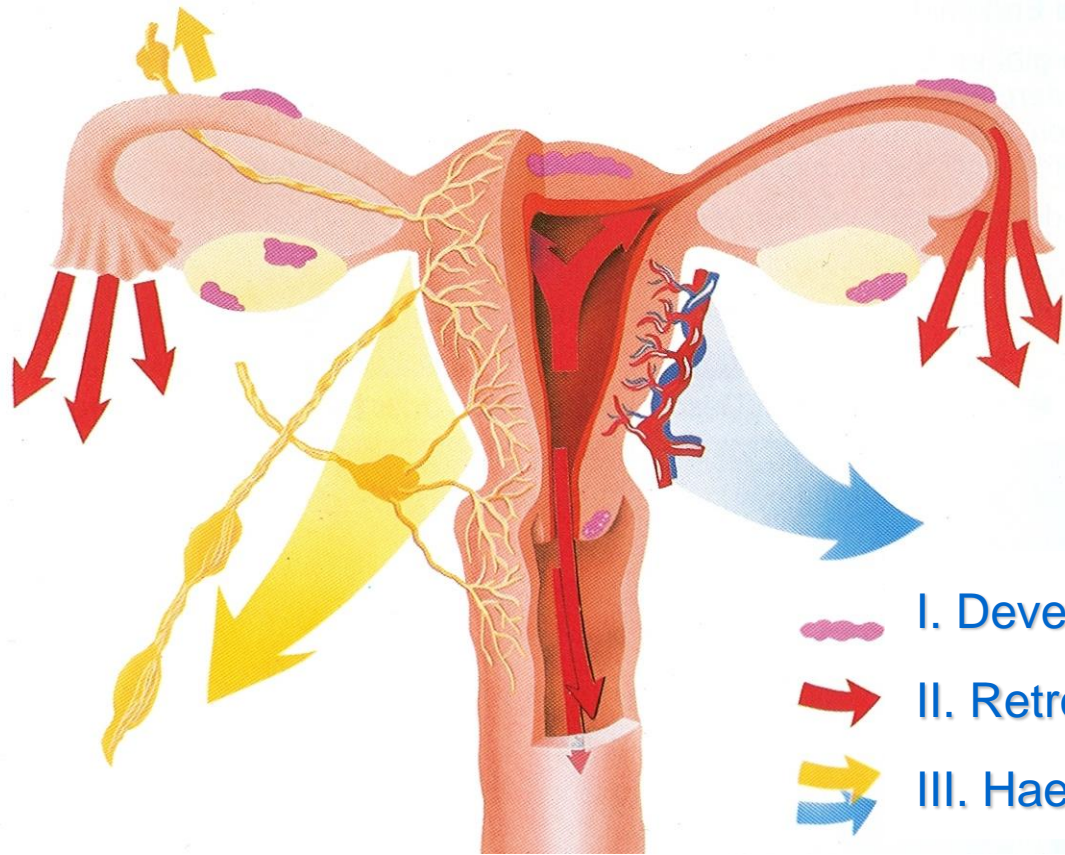
Post-sterilisation status

Peritoneal factor

Pelvic adhesions

Endometriosis

Pathogenesis of Endometriosis

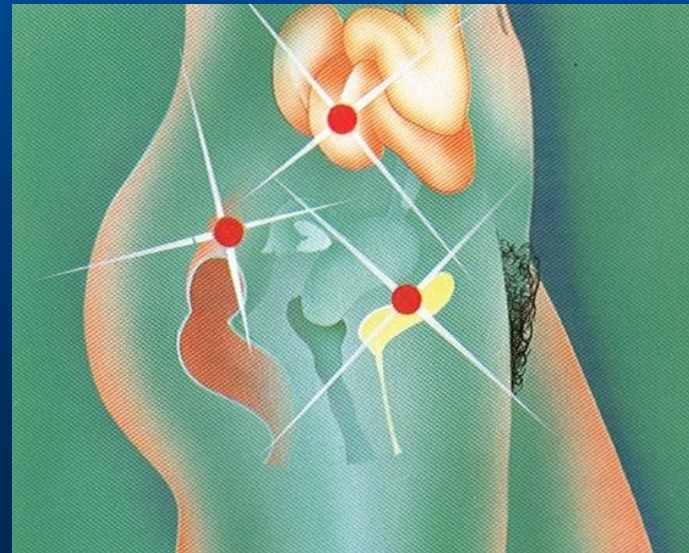
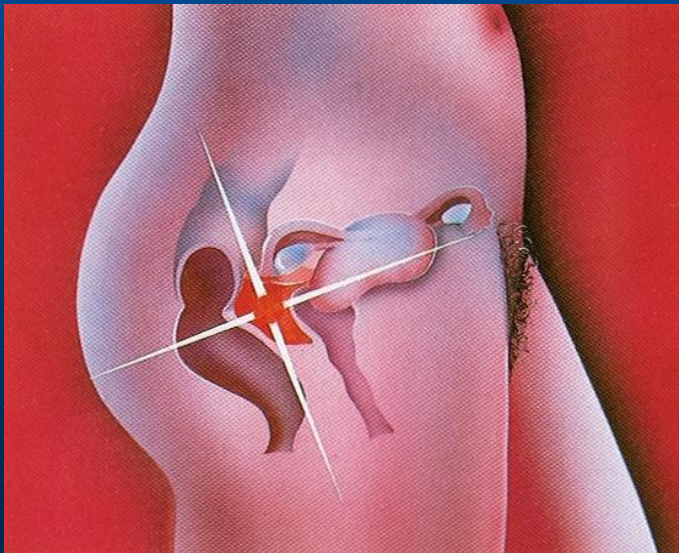
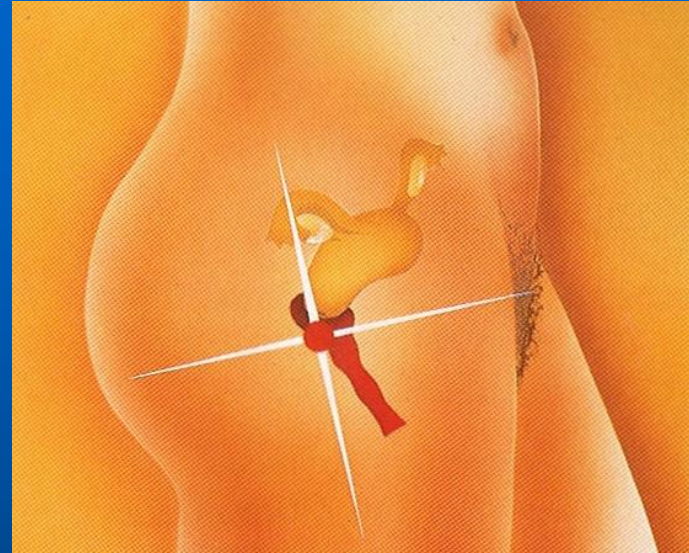


- I. Development of female genital tract
- II. Retrograd menstruation
- III. Haematogen, lymphogen propagation

Peritoneal Endometriosis Laparoscopic View



Location of Endometriosis



Causes of Male Infertility

Pretesticular

Chromosomal (Klinefelter-syndrome)
Coitus/erectile dysfunction
Ejaculation disturbances

Hormonal (hypogonadotropic hypogonadismus, hyperprolactinaemia)

Testicular

Congenital (cryptorchismus, immotile cilia syndrome)
Infectiv (orchitis)

Vascular (torsio, varicocele)
Antispermato-genic agents (chemotherapy, drugs, heat)

Posttesticular

Obstructive (epididymal, vasal)
Epididymitis

Immunological factors

Investigation of Infertility I.

First visit

Weight kg Height m

Galactorrhoea Acne Hirsutism

Cyt Kolp vag. fluid Uterus Adnexum (right) Adnexum (left)

Bimanual examination

TVS

Anamnesis

General history:

Laparotomy (date):

Gynaecologic operation
(type, date):

Delivery (date):

Abortion (date):

Extrauterine gravidity (date):

Investigation of Infertility

Ovarian factor

right ovary +/- left ovary +/-
 cycle length day duration of bleeding day
 basal body temperature curve: biphasic/monophasic
 LH-peak: cycle day ovulatory cycle: yes/no
 LH: FSH: LH/FSH:
 T: DHEAS: SHBG:
 E2: P:
 TSH basal: stimulated:
 basal: stimulated:

Gonadotrophins

Androgens

Corpus luteum function

Thyroid function

Prolactin

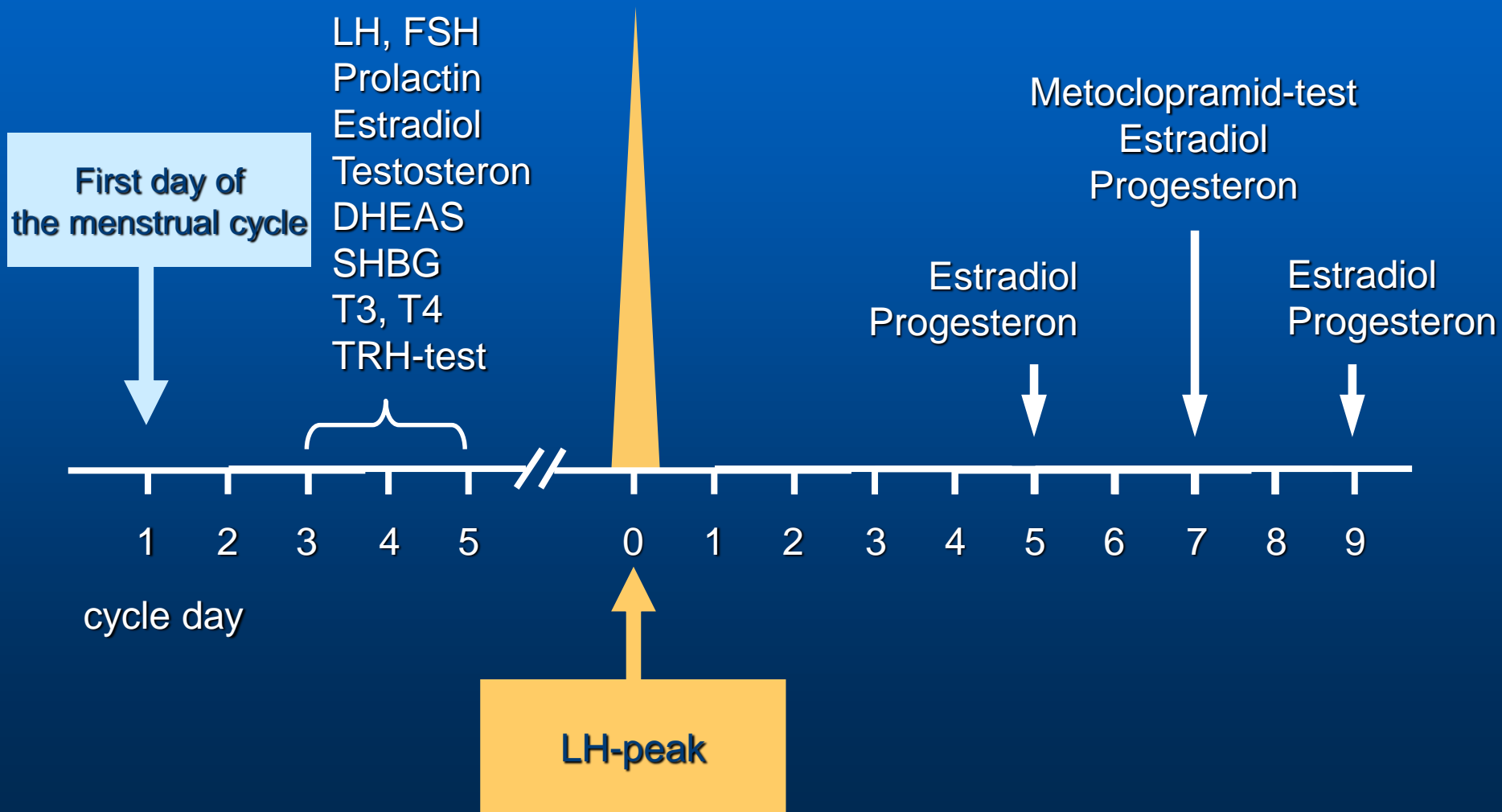
Tubal factor

last HSG: last laparoscopy:
 right tube patent yes/no
 left tube patent yes/no
 uterine cavity: normal/abnormal

Andrological factor

	sperm count (mill/ml)	motility (% good mot.)	morphology (% norm.)
Assessment I.:	<input type="text"/>	<input type="text"/>	<input type="text"/>
Assessment II.:	<input type="text"/>	<input type="text"/>	<input type="text"/>
After preparation:	<input type="text"/>	<input type="text"/>	<input type="text"/>

Hormonal Assessment of the Ovarian Factor



Prevalence of Endocrine Disorders Among Patients of the Division of Assisted Reproduction, I. Dept. of Obstetrics and Gynaecology, Semmelweis University (n=498)

Hormone	Endocrine disorder	Frequency %
LH	elevated LH-level	7
FSH	elevated FSH-level	13
LH/FSH	elevated LH/FSH-ratio	3
Prolactin	hyperprolactinemia	
	latent	34
	manifest	12
TSH	hypothyreosis	
	latent	24
	manifest	8
DHEAS	hyperthyreosis	1
Testosteron	hyperandrogenemia	29
Progesteron	hyperandrogenemia	2
	corpus luteum insuff.	58

Investigation of Infertility

Ovarian factor

right ovary +/- left ovary +/-
 cycle length day duration of bleeding day
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 basal: stimulated:

Gonadotrophins

Androgens

Corpus luteum function

Thyroid function

Prolactin

Tubal factor

right tube patent

left tube patent

uterine cavity:

last HSG: last laparoscopy:
 yes/no yes/no
 yes/no yes/no
 normal/abnormal

Andrological factor

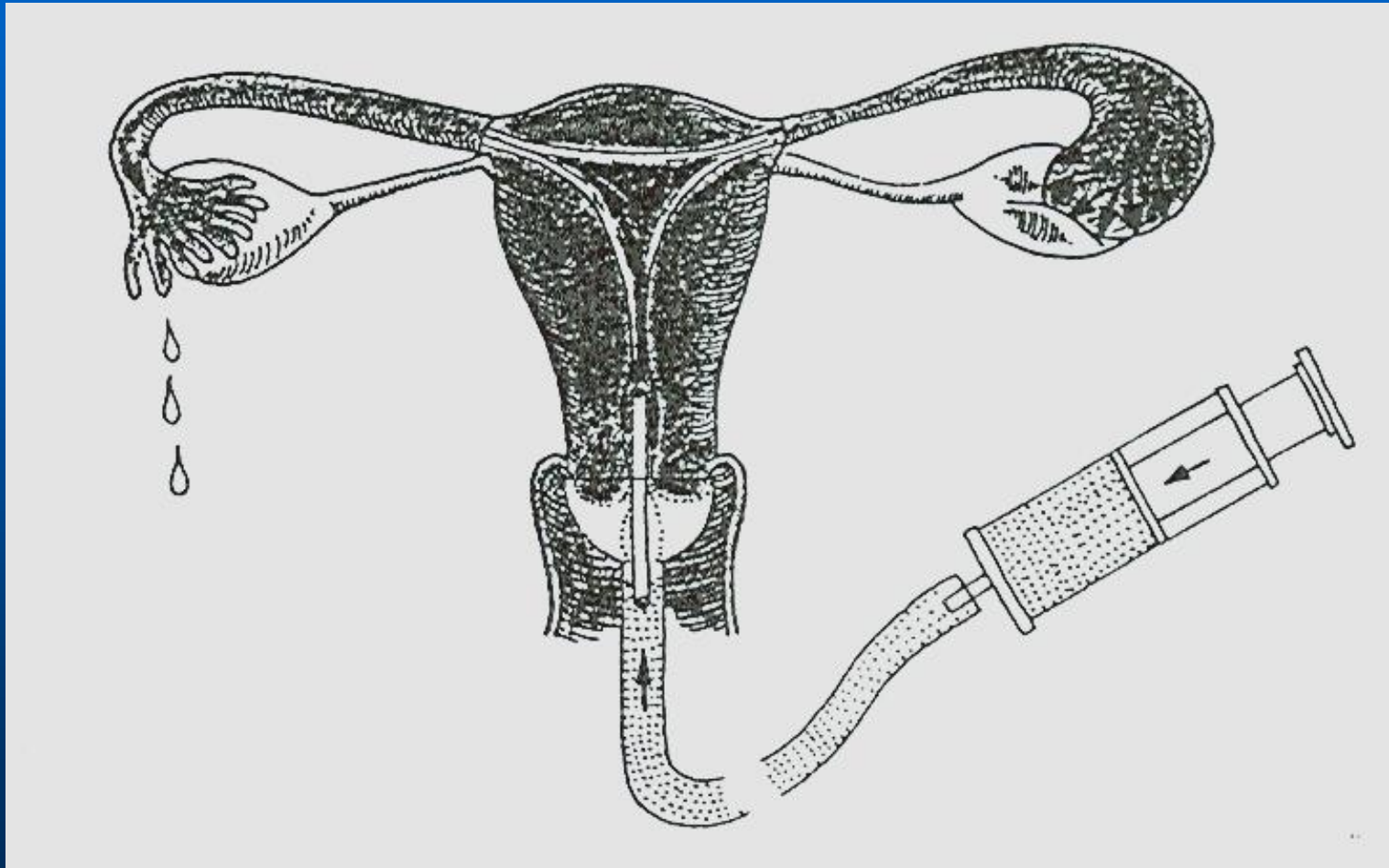
sperm count
(mill/ml)

motility
(% good mot.)

morphology
(% norm.)

Assessment I.:
 Assessment II.:
 After preparation:

Hysterosalpingography (HSG)

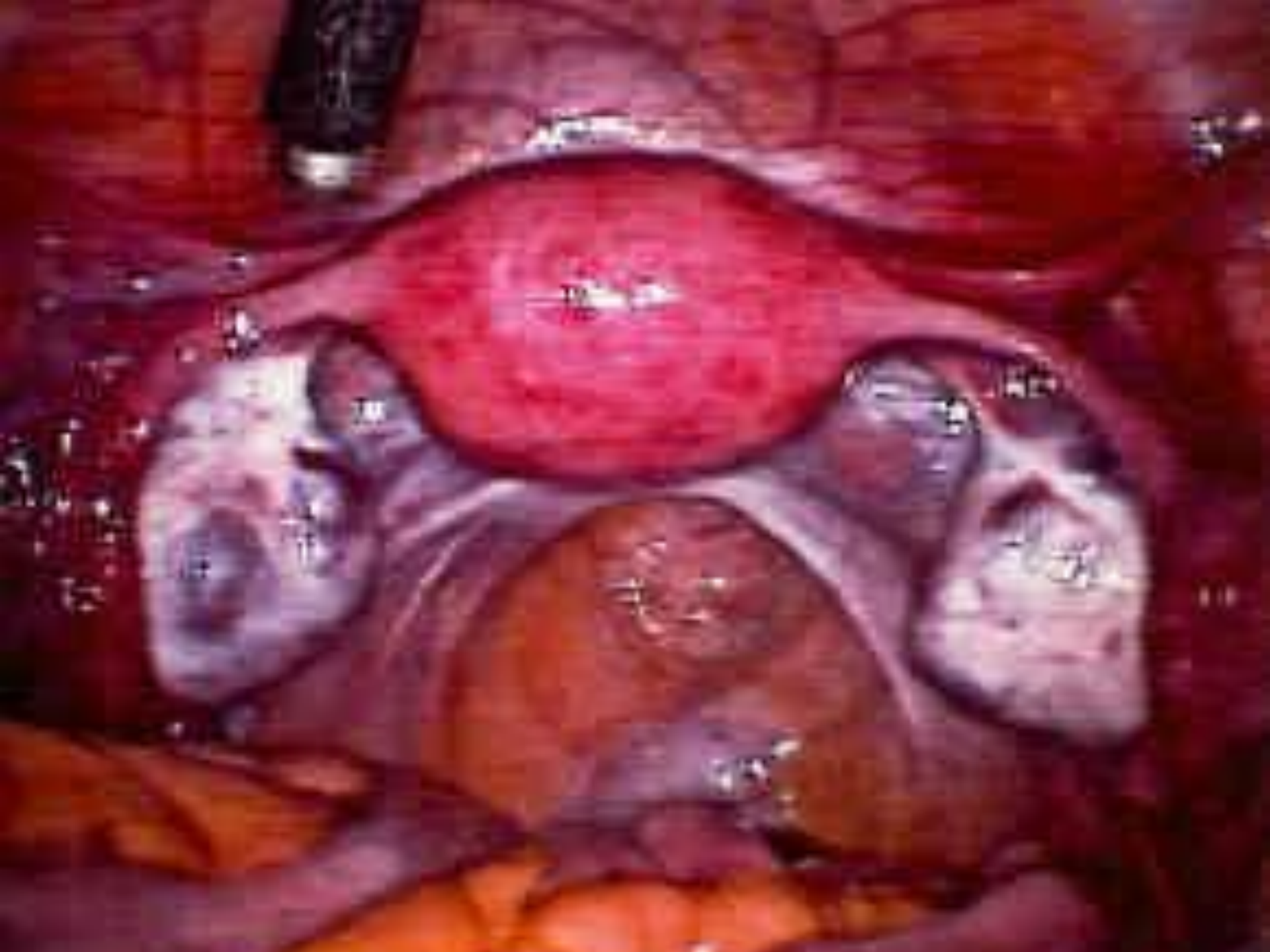


Normal and Pathological HSG Picture

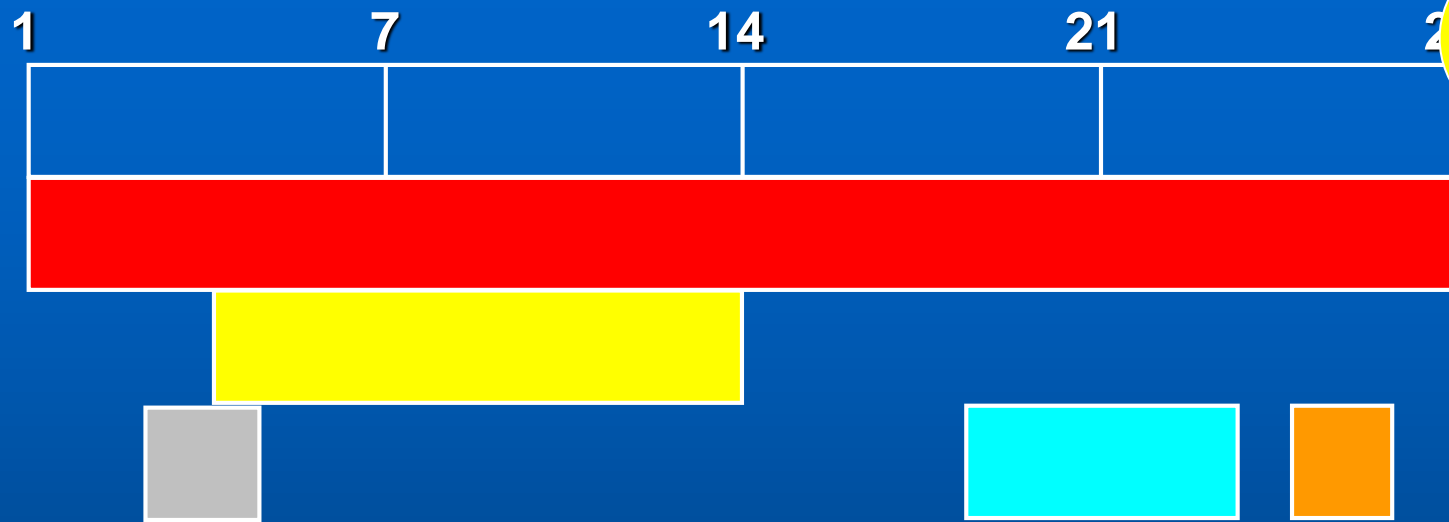


Laparoscopy





Investigation of Female Infertility




 Basal body temperature

 Serum Progesteron/Prolactin

 Hysterosalpingography

 Endometrium biopsy

 Serum FSH, LH, DHEAS, T,
TRH-test (TSH, Prolactin)

Investigation of Infertility

Ovarian factor

right ovary +/- left ovary +/-
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Corpus luteum function

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right tube patent

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uterine cavity:

last HSG: last laparoscopy:
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 normal/abnormal

Andrological factor

sperm count
(mill/ml)

motility
(% good mot.)

morphology
(% norm.)

Assessment I.:
 Assessment II.:
 After preparation:

Normal Spermogram

Sperm

count	≥ 20 million/ml
motility	$\geq 50\%$ motile
kvantitative motility	$\geq 25\%$ very good motility $< 50\%$ immotile
morphology	$\geq 30\%$ normal morphology

Terminology of Pathologic Spermogram

Spermia

	= volume
aspermia	= no semen
hypospermia	= less than 2ml semen

Zoospermia

	= spermium in the semen
azoospermia	= no spermium in the semen sample
cryptozoospermia	= very low spermium count
oligozoospermia	= < 20 million spermium/ml
polyzoospermia	= > 250 million spermium/ml
asthemozoospermia	= low motility (< 50%)
teratozoospermia	= proportion of abnormal spermium > 50%
necrozoospermia	= all spermium necrotized

Definition of Assisted Reproduction

(= treatment of infertility)

Forms of Assisted Reproduction

Wider sense

Terminated intercourse

Ovarian stimulation

Intrauterin insemination

Operative treatment

In vitro fertilization and embryotransfer (= IVF-ET)

Narrow sense

In vitro fertilization and embryotransfer (= IVF-ET)

Treatment of Ovulation Disorders (Drugs for Controlled Ovarian Stimulation)

Antiestrogens

Clomiphene-citrate

Gonadotrophins

Urogonadotrophins

Human menopausal gonadotrophin (HMG)

Purified follicle stimulating hormone (FSH)

Human choriogonadotrophin (hCG)

Recombinant gonadotrophins



Treatment of Ovulation Disorders (Drugs for Controlled Ovarian Stimulation)

Antiestrogens

Clomiphene-citrate

Gonadotrophins

Urogonadotrophins

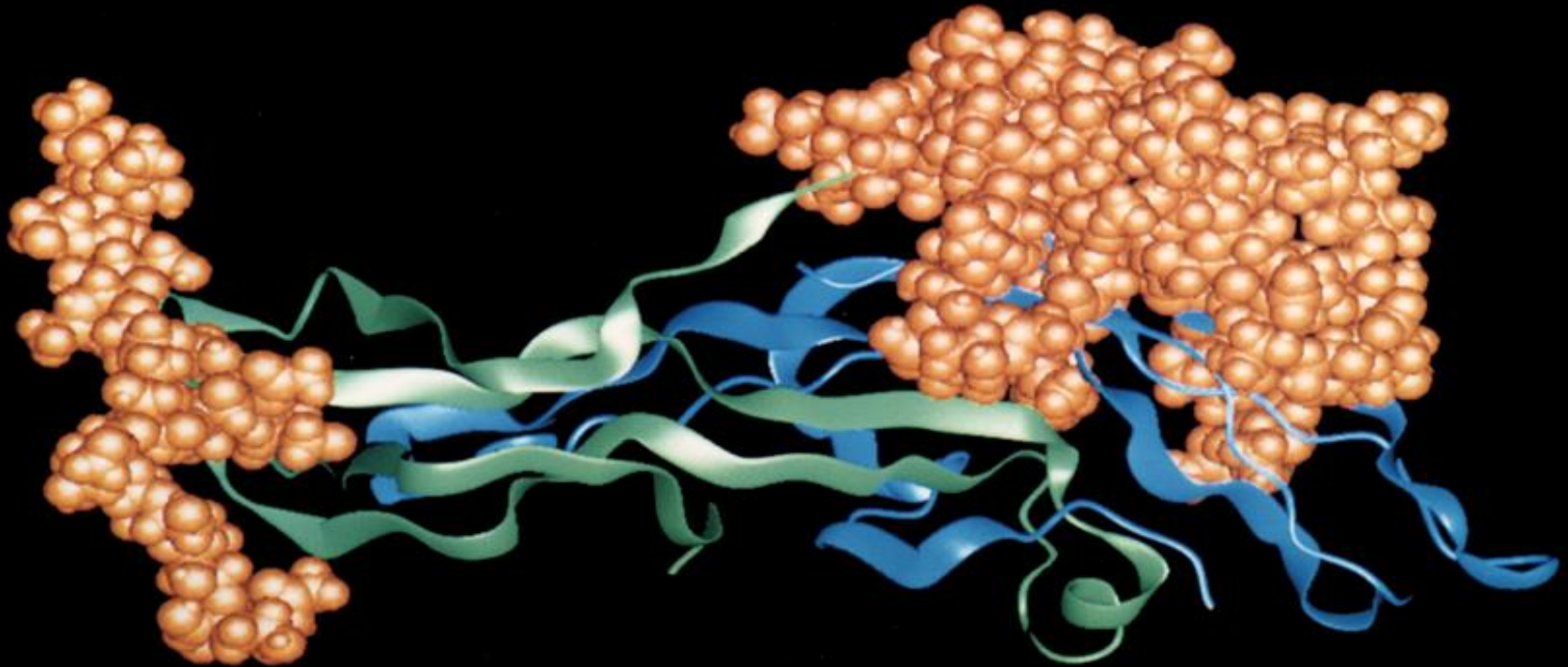
Human menopausal gonadotrophin (HMG)

Purified follicle stimulating hormone (FSH)

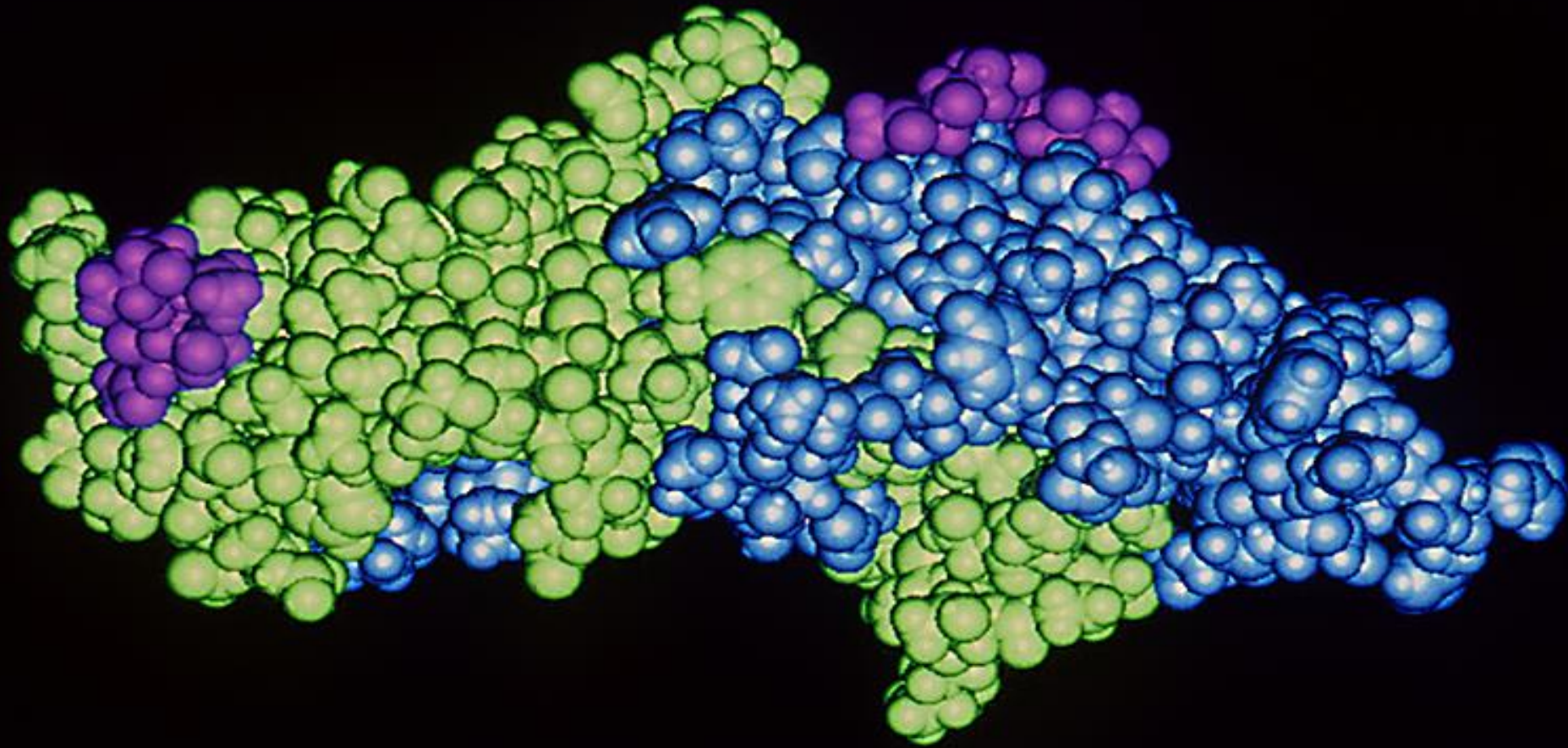
Human chorionic gonadotrophin (hCG)

Recombinant gonadotrophins

Chemical Structure of Follicle Stimulating Hormone (FSH)



Chemical Structure of Recombinant FSH



Treatment of Ovulation Disorders

(Drugs for Controlled Ovarian Stimulation)

	Agent	Product
Antiestrogens	Clomiphene-citrate 50mg	Clostilbegyt tabl.
	Clomiphene-citrate 50mg	Serophene tabl.

Gonadotrophins

Urogonadotrophins

Human menopausal gonadotrophin (HMG) products

FSH+LH 75-75 IU	Menogon inj.
FSH+LH 75-75 IU	Menopur inj.
FSH+LH 75-75 IU/150-150 IU	Merional inj.

Purified Follicle Stimulating Hormone (FSH) products

FSH urofollitropin 75/150 IU	Fostimon HP inj.
FSH urofollitropin 75 IU	Metrodin HP inj.

Human Choriogonadotrophin (hCG) products

hCG 1500/5000 IU	Choragon inj.
hCG 1500 IU	Choragonin inj.
hCG 1500/2000/5000 IU	Choriomon inj.
hCG 2000/5000 IU	Profasi inj.

Recombinant gonadotrophins

recFSH 37,5/75/150 IU	Gonal-F inj.
recFSH 50/100 IU	Puregon inj.
recLH 75 IU	Luveris inj.

Hypothalamus

 **GnRH**

Hypophysis

 **LH/FSH**

Ovary

Clomiphene-citrate

Dosage:

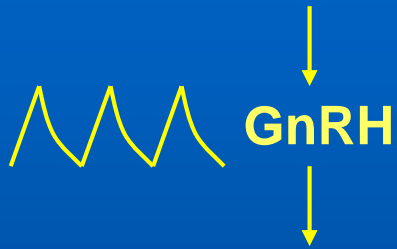
50-150 mg/day

from 3-5. cycle day
for 5 days.

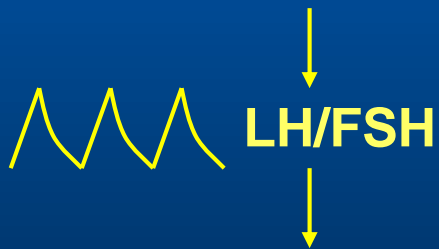
Disadvantage:

low number of follicles
unfavorable effect on
endometrium

Hypothalamus



Hypophysis



Ovary

Dosage:

from 3-5. cycle day

1-2 ampule/day

Individual protocol depending on patients response to therapy

**Human Menopausal
Gonadotrophin (HMG)**



Hypothalamus

 **GnRH**

Hypophysis

 **LH/FSH**

Ovary

**Clomiphene-citrate +
HMG**

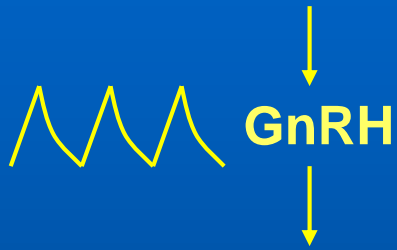
Dosage:

simultaneously

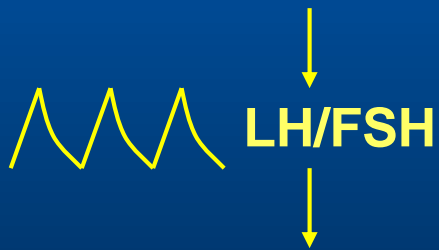
sequentially



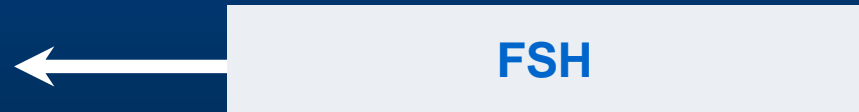
Hypothalamus



Hypophysis



Ovary



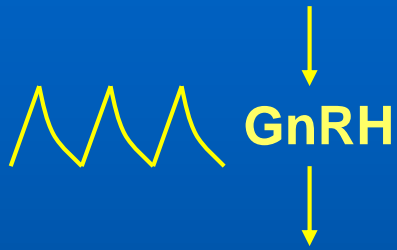
Indication:

elevated serum
LH, LH/FSH, androgen
levels
(eg. PCOS)

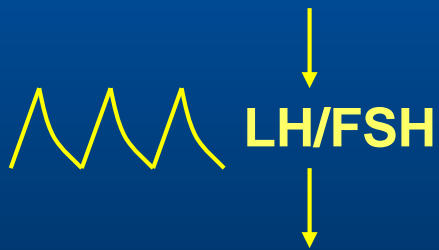
Dosage:

from 3-5. cycle day
1-2 ampule/day

Hypothalamus



Hypophysis



Ovary



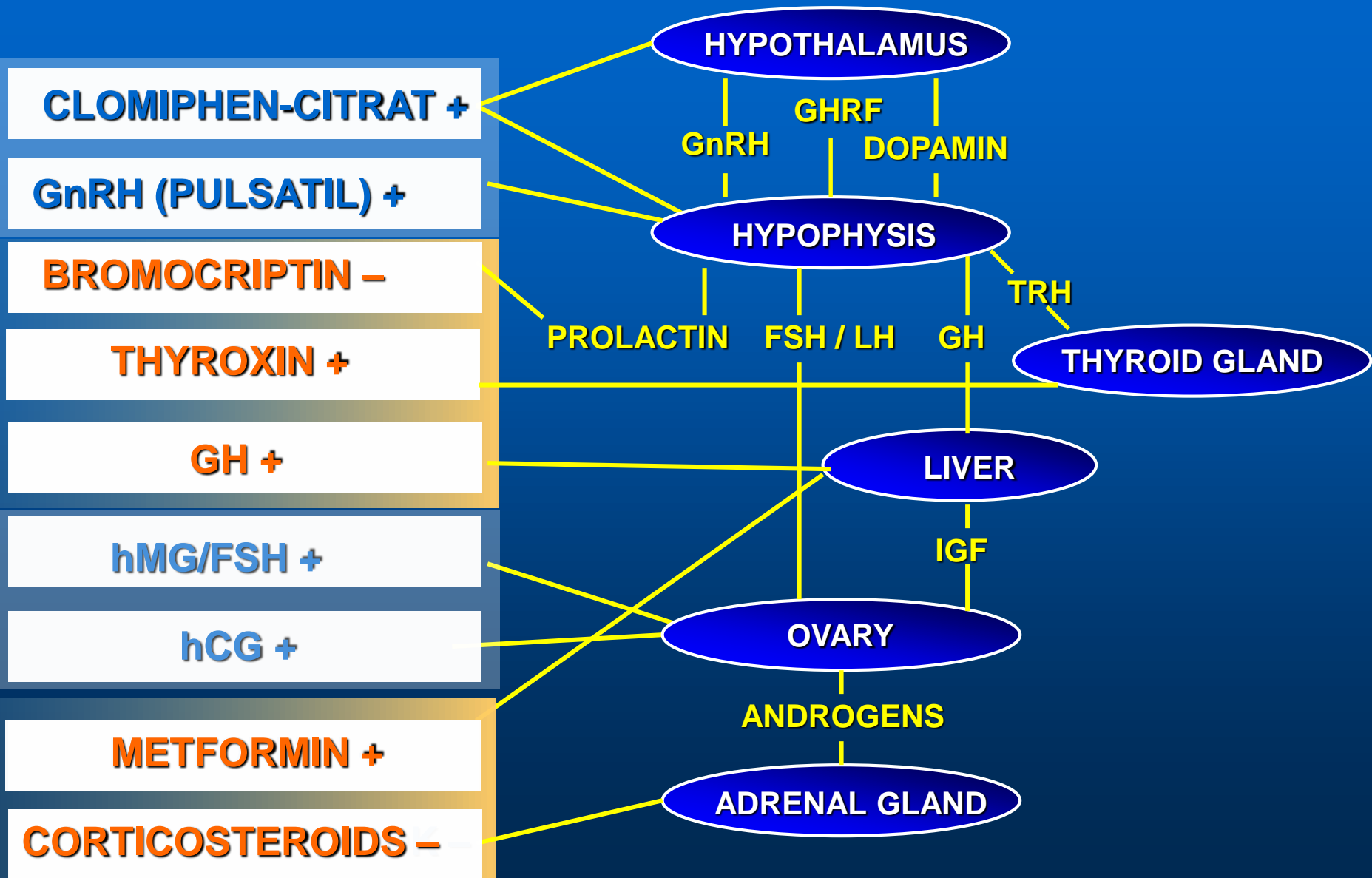
Indication:

hypothalamic
amenorrhoea

Dosage:

10-20 μg /60-90 min
infusion pump

Ovarian Stimulation for Anovulatory Infertility



Treatment of Andrological Infertility

Medical or operative treatment:

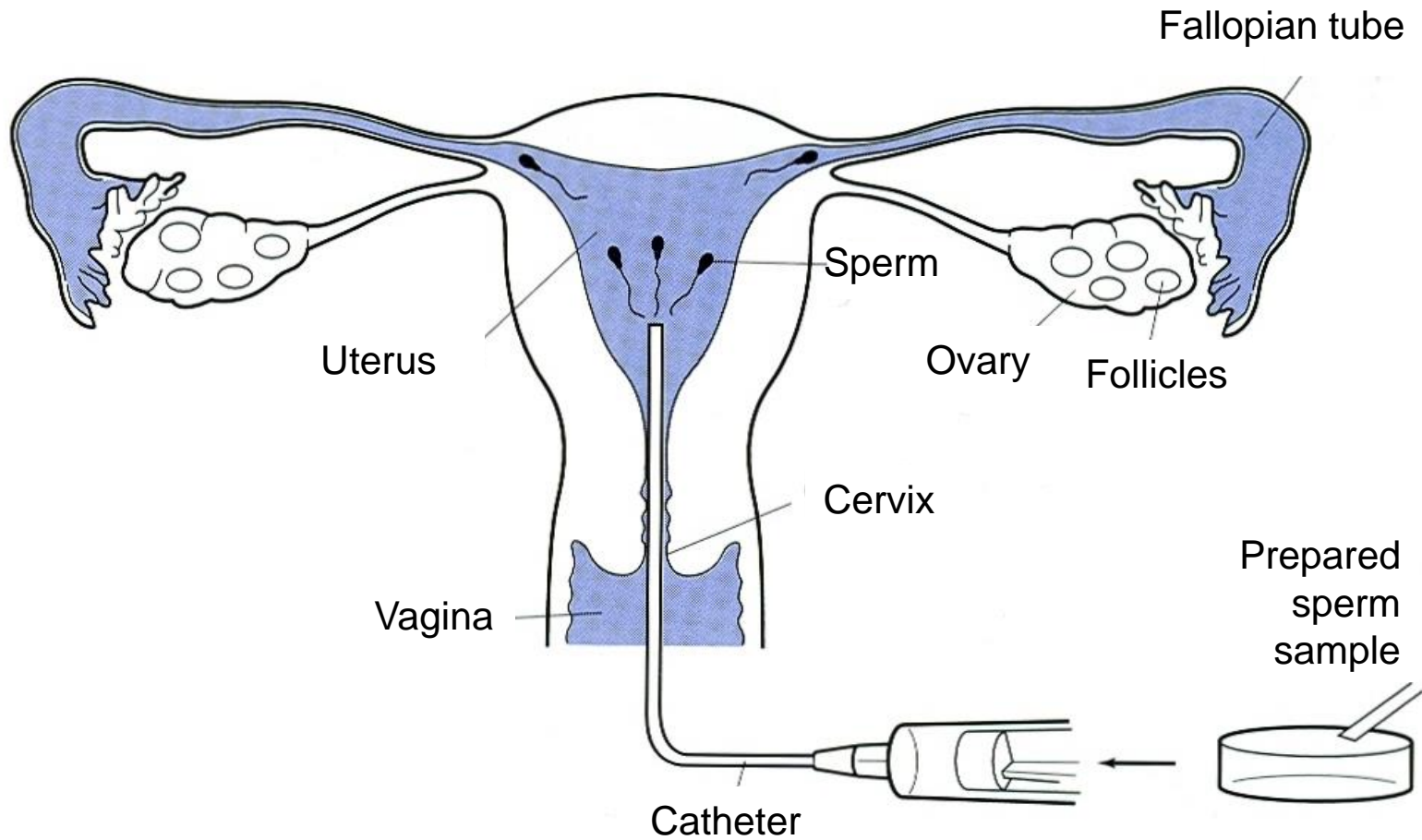
sperm count/motility/morphology will not be better

Solution:

Intrauterin insemination

In vitro fertilization and embryotransfer

Intrauterin Insemination (IUI)



Treatment of Female Infertility of Anatomical Origin

Uterine malformation

Metroplasty

Myoma

Myomectomy

Endometriosis

Electrocoagulation

Cystectomy

Drugs

Gestagens

Oral anticoncipients (monophasic)

Danazol

GnRH-agonists

Fallopian tube disorders

Treatment of Tubal Infertility

Operative

peritubaric adhaesiolysis, salpingolysis

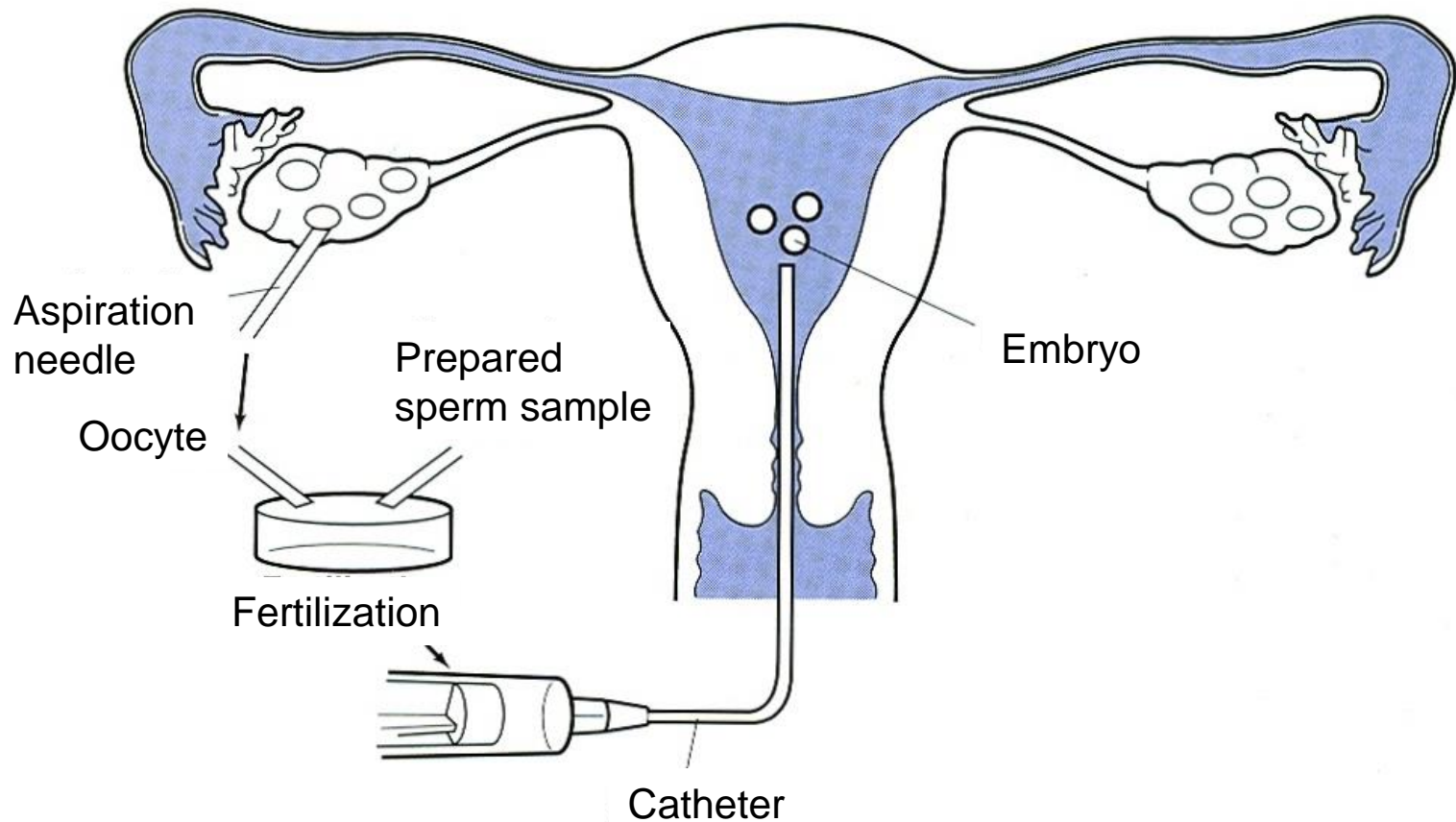
salpingoneostomy, fimbrioplasty

tubotubaric reanastomosis

tubouterinal implantation

In vitro fertilization and embryo transfer (IVF-ET)

In Vitro Fertilization and Embryotransfer (IVF-ET)



Pioneers in IVF

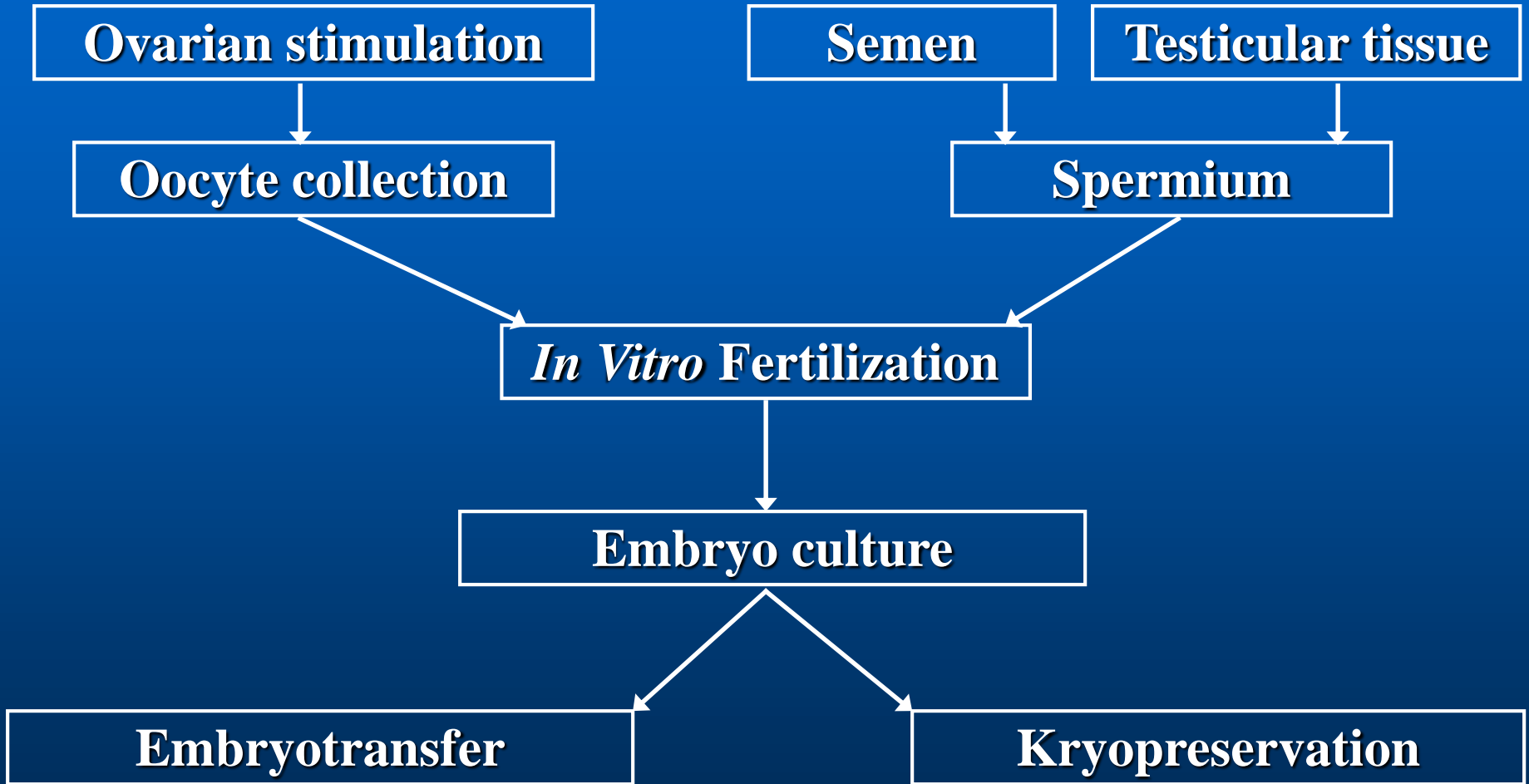
Edwards & Steptoe

(1978)



Definitions

OOCYTE	oocyte	from oocyte pick-up to fertilization
ZYGOTE (Pronucleus - PN-state)	fertilized oocyte	from fertilization to 1. cleavage
PRAEEMBRYO	Preembryo	from 1. cleavage to the 14. day
EMBRYO	Embryo	from 14. day to 12. week
FETUS	fetus	from 12. week to birth



Ovarian stimulation

Semen

Testicular tissue

Oocyte collection

Spermium

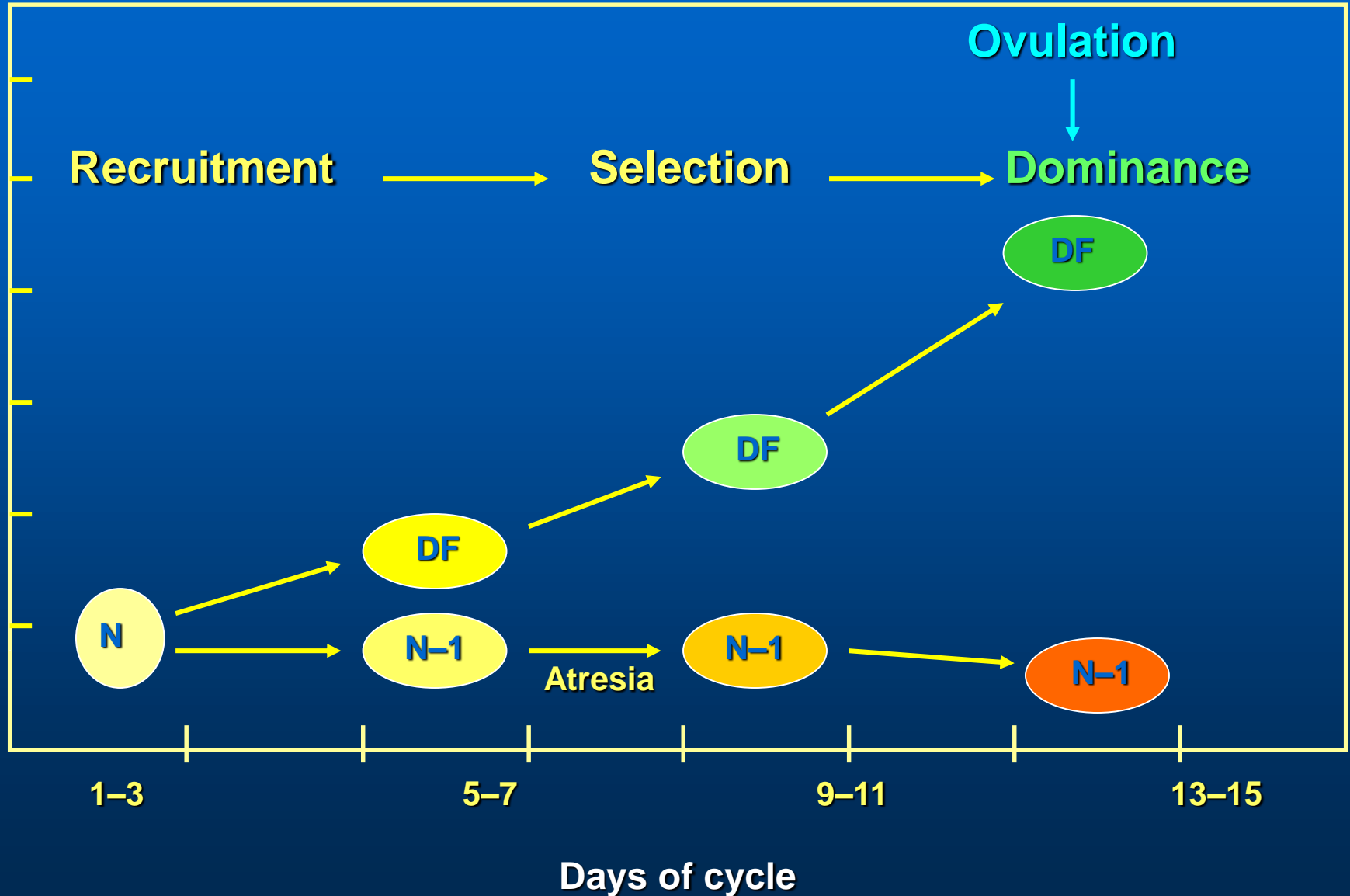
***In Vitro* Fertilization**

Embryo culture

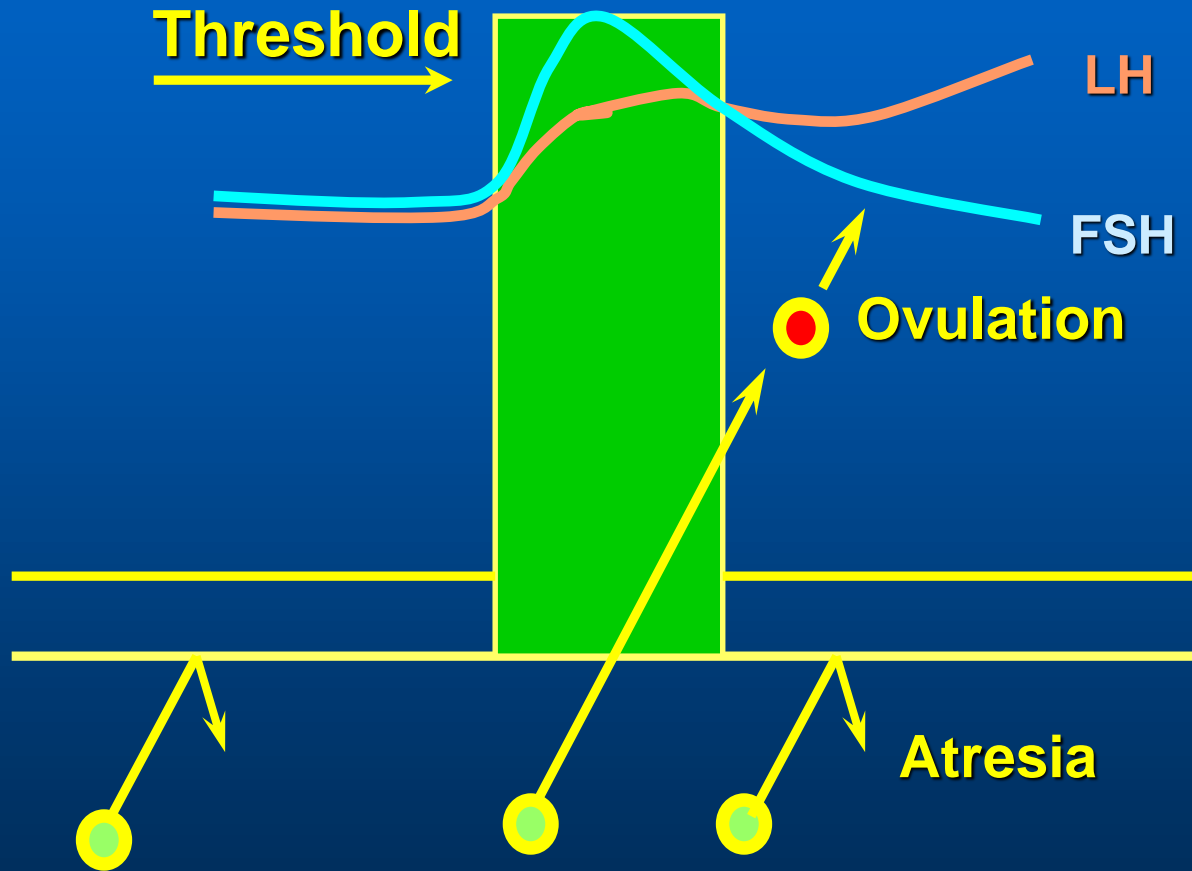
Embryotransfer

Kryopreservation

Selection of the Dominant Follicle during the Menstrual Cycle

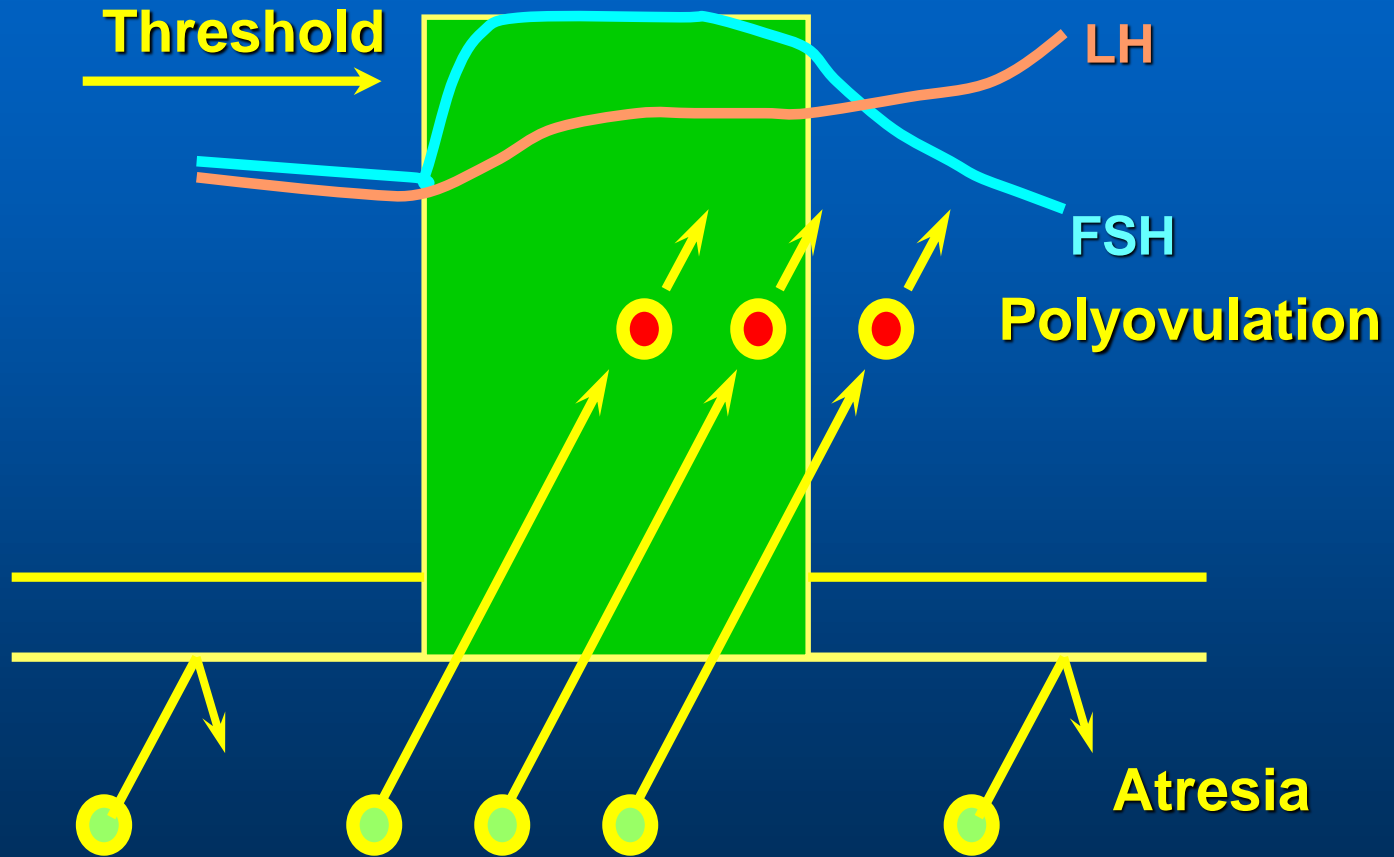


Monoovulation - FSH-gate



Baird (1987)

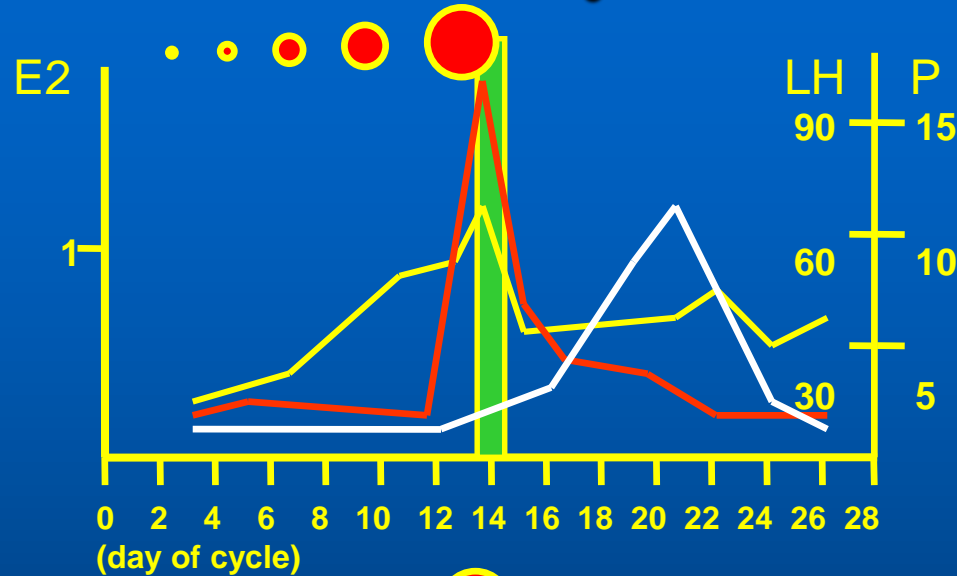
Polyovulation – Wider FSH-gate



Baird (1987)

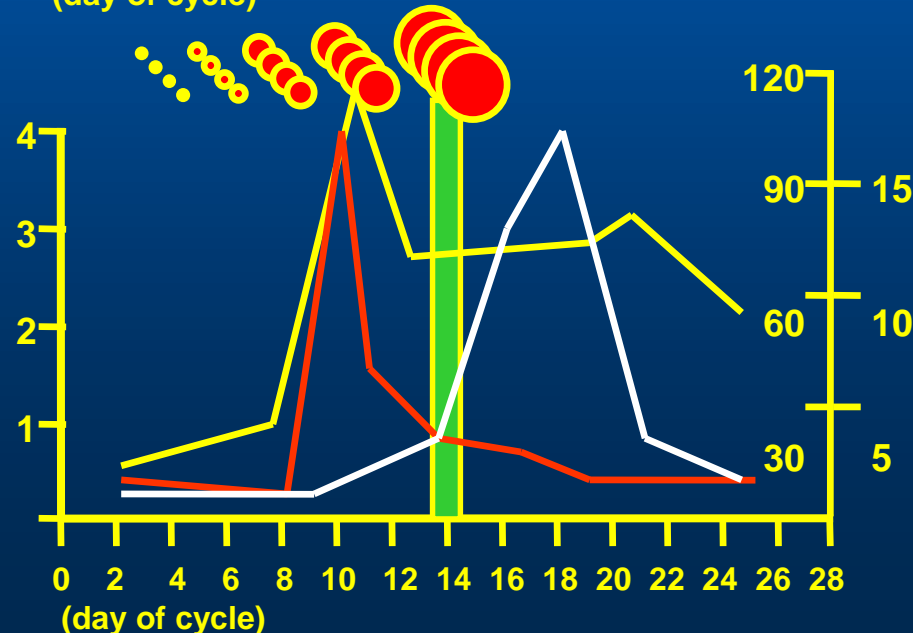
Hormon Levels in Spontaneous and Stimulated Cycles

Spontaneous cycle

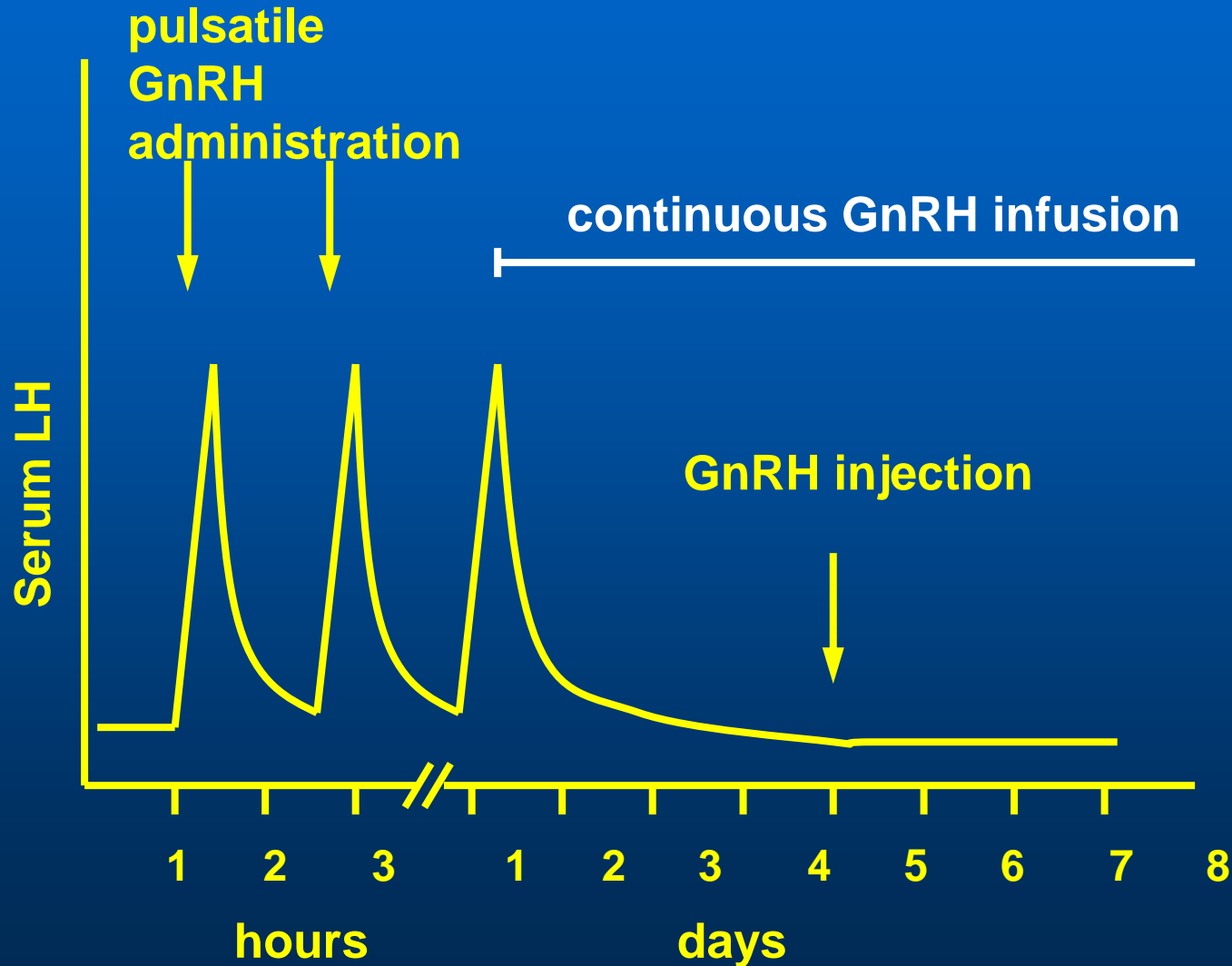


Estradiol (E2) (nmol/l) — Yellow line
 LH (mIU/ml) — Red line
 Progesterone (P) (nmol/l) — White line

Stimulated cycle



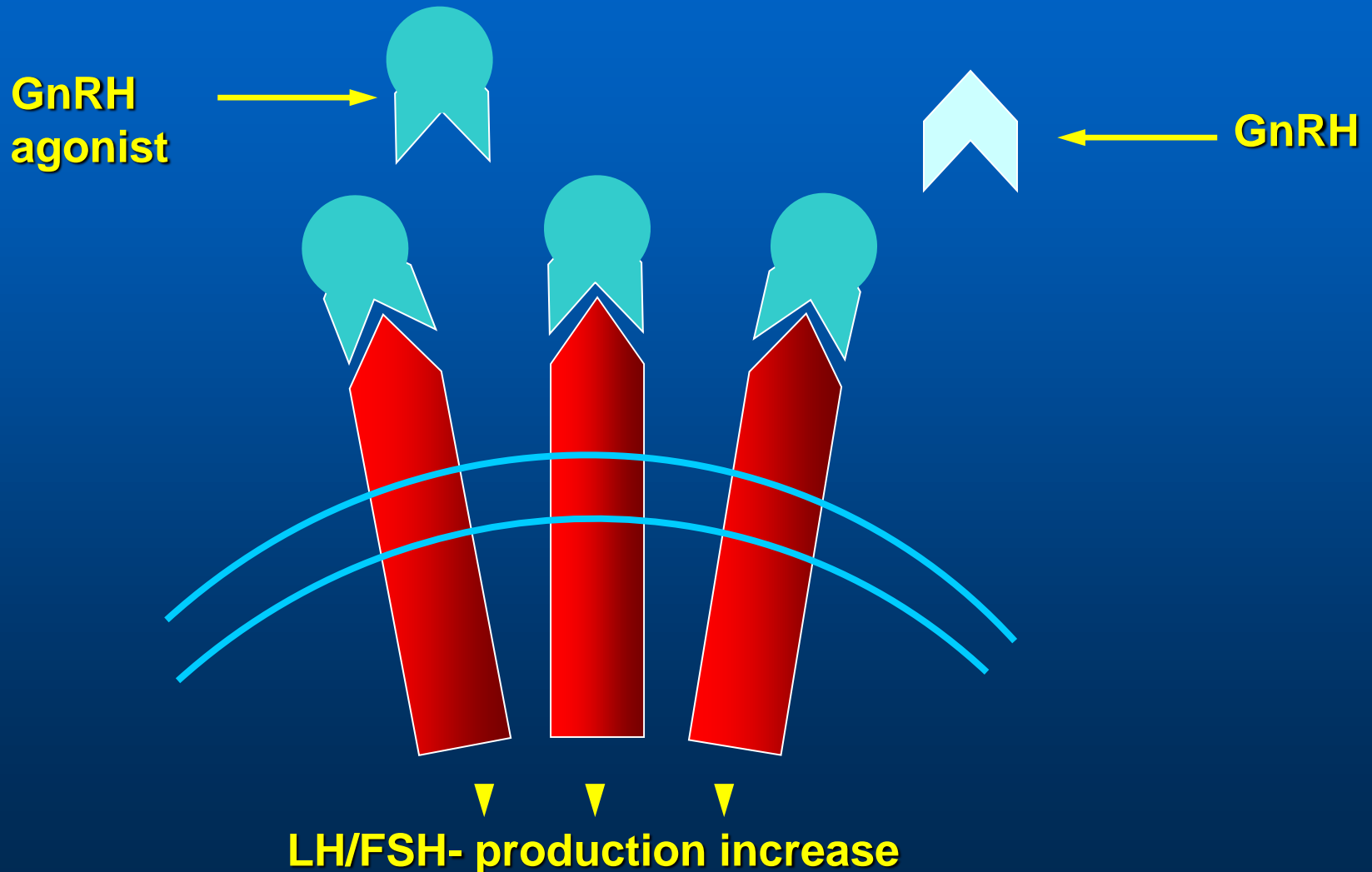
Effect of Pulsatile/Continuous GnRH Administration on LH Release



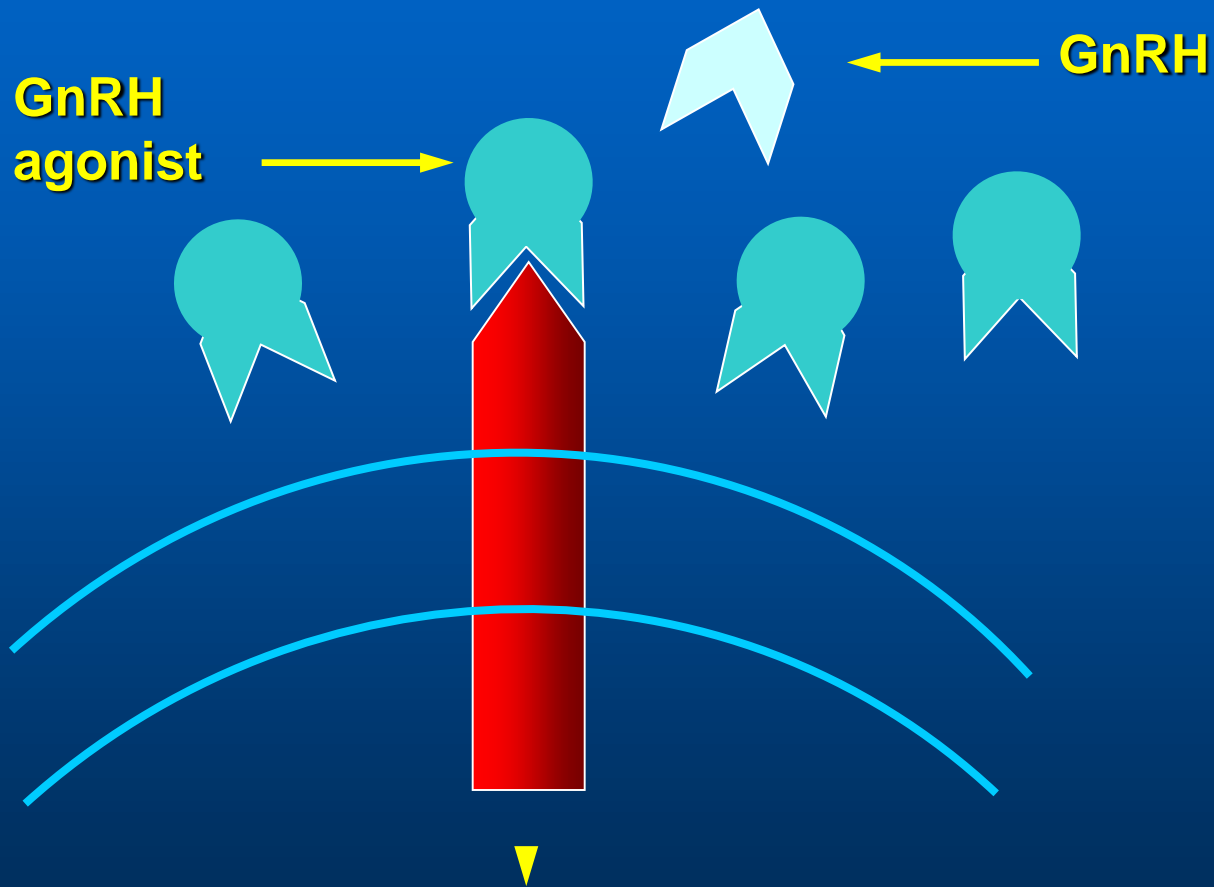
Chemical Structure of GnRH-agonists

	Conformation										Relative efficacy
	1	2	3	4	5	6	7	8	9	10	
GnRH	PGlu	His	Trp	Ser	Tyr	Gly	Leu	Arg	Pro	Gly-NH ₂	1
Buserelin						D-Ser (TBU)				Ethylamide	100
Nafarelin						D-(2-Nal)					100
Leuprolide						D-Leu				Ethylamide	50
Goserelin						D-Ser (TBU)				Az-Gly-NH ₂	50
Decapeptyl						D-Trp					100
Histrelin						D-His (BZI)				Ethylamide	100

GnRH-agonistic Effect – Early Phase, Stimulation



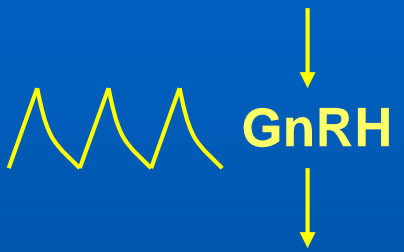
GnRH-agonistic Effect – Chronic, Suppression



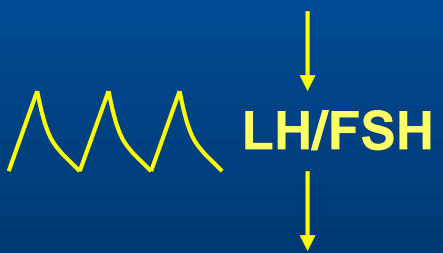
Receptor count decrease (down-regulation)

GnRH agonist displaces native GnRH-molecule on receptor
(desensitization)

Hypothalamus



Hypophysis



Ovary

GnRH-agonist + HMG



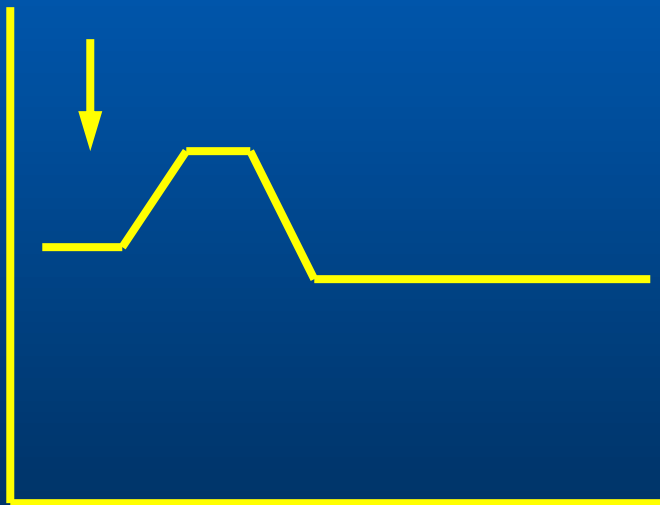
GnRH-agonist + Gonadotrophin Stimulation



Effect of GnRH-agonists and -antagonists

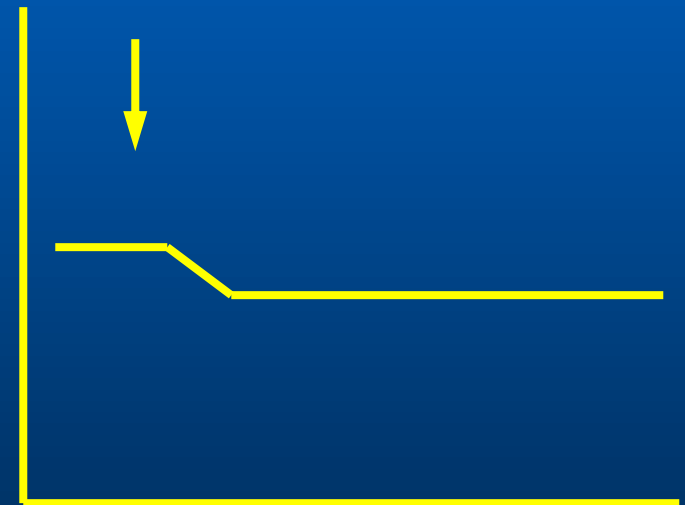
AGONIST

LH
FSH
E₂
P₄
T



ANTAGONIST

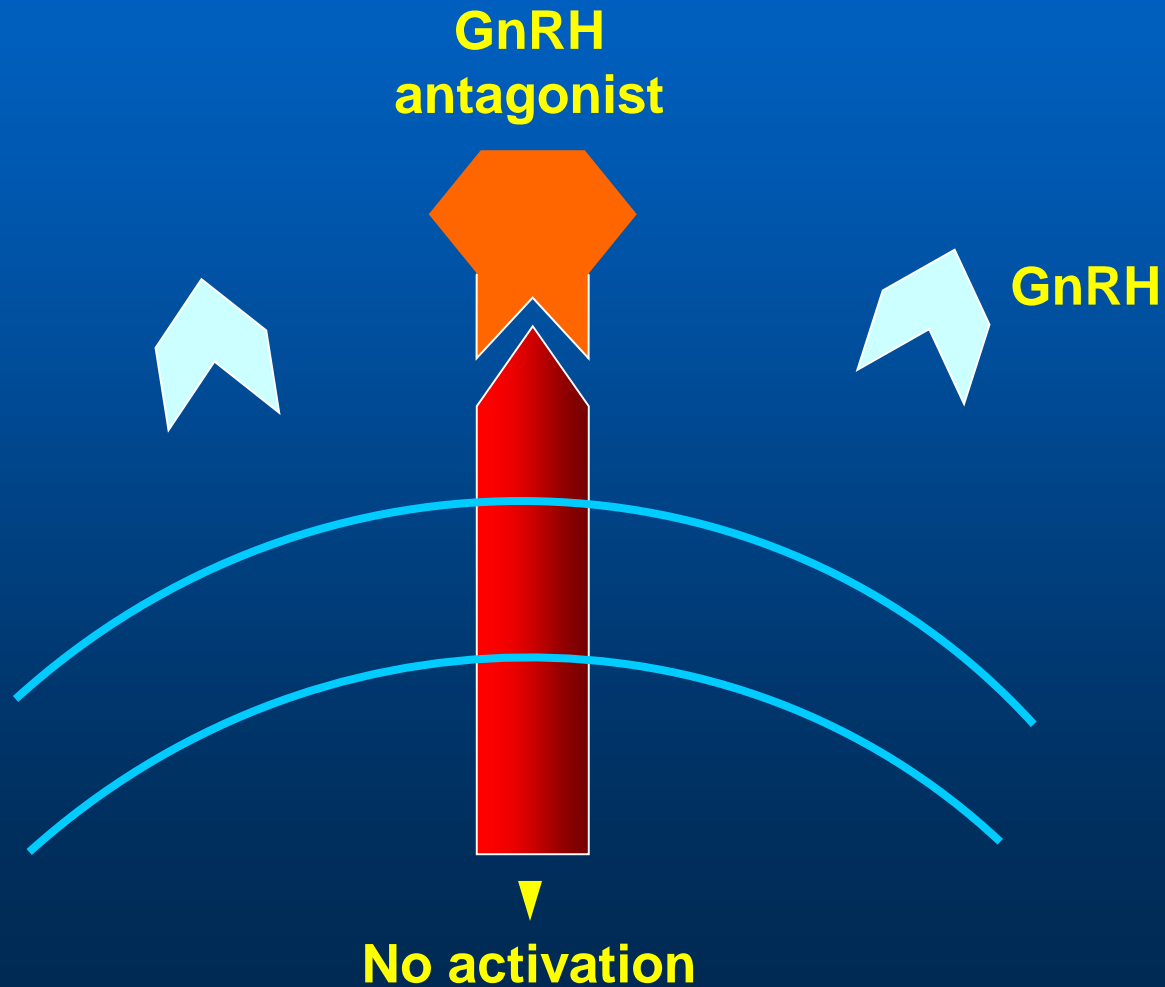
LH
FSH
E₂
P₄
T



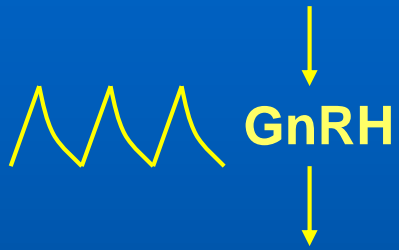
Chemical Structure of GnRH-antagonists

	1	2	3	4	5	6	7	8	9	10
GnRH	pyro Glu	His	Trp	Ser	Tyr	Gly	Leu	Arg	Pro	Gly NH ₂
First generation										
Phe-Ala	pyro Glu	D-Phe	Trp	Ser	Tyr	D-Ala	Leu	Arg	Pro	Gly NH ₂
Phe-Trp-Phe	pyro Glu	D-Phe	D-Trp	Ser	Tyr	D-Phe	Leu	Arg	Pro	Gly NH ₂
Nal-Arg	AcD-Nal	D4F Phe	D-Trp	Ser	Tyr	D-Arg	Leu	Arg	Pro	D-Ala
Diterix	AcD-Nal	D4C phe	D-Trp	Ser	Tyr	Db-Arg	Leu	Arg	Pro	D-Ala
Second generation										
Nal-Glu	AcD-Nal	D4Ci Phe	D-Pal	Ser	Arg	D-Glu (AA)	Leu	Arg	Pro	D-Ala
Third generation										
Antide	AcD-Nal	D4Ci Phe	D-Pal	Ser	Nic-Lys	D-Nic Lys	Leu	Ipr Lys	Pro	D-Ala
Azaline B	AcD-Nal	D4Ci Phe	D-Pal	Ser	Aph (atz)	Aph (atz)	Leu	Ipr Lys	Pro	D-Ala
A-75998	AcD-Nal	D4Ci Phe	D-Pal	Ser	N-Me Iyr	D-Nic Lys	Leu	Ipr Lys	Pro	D-Ala
Ganirelix	AcD-Nal	D4Ci Phe	D-Pal	Ser	Tyr	Db-Arg	Leu	Db-Arg	Pro	D-Ala
Cetrorelix	AcD-Nal	D4Ci Phe	D-Pal	Ser	Tyr	D-cit	Leu	<u>Arg</u>	Pro	D-Ala

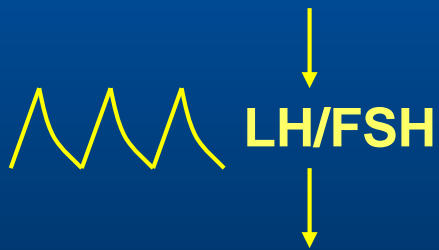
GnRH-antagonistic Effect - Immediate Suppression



Hypothalamus



Hypophysis

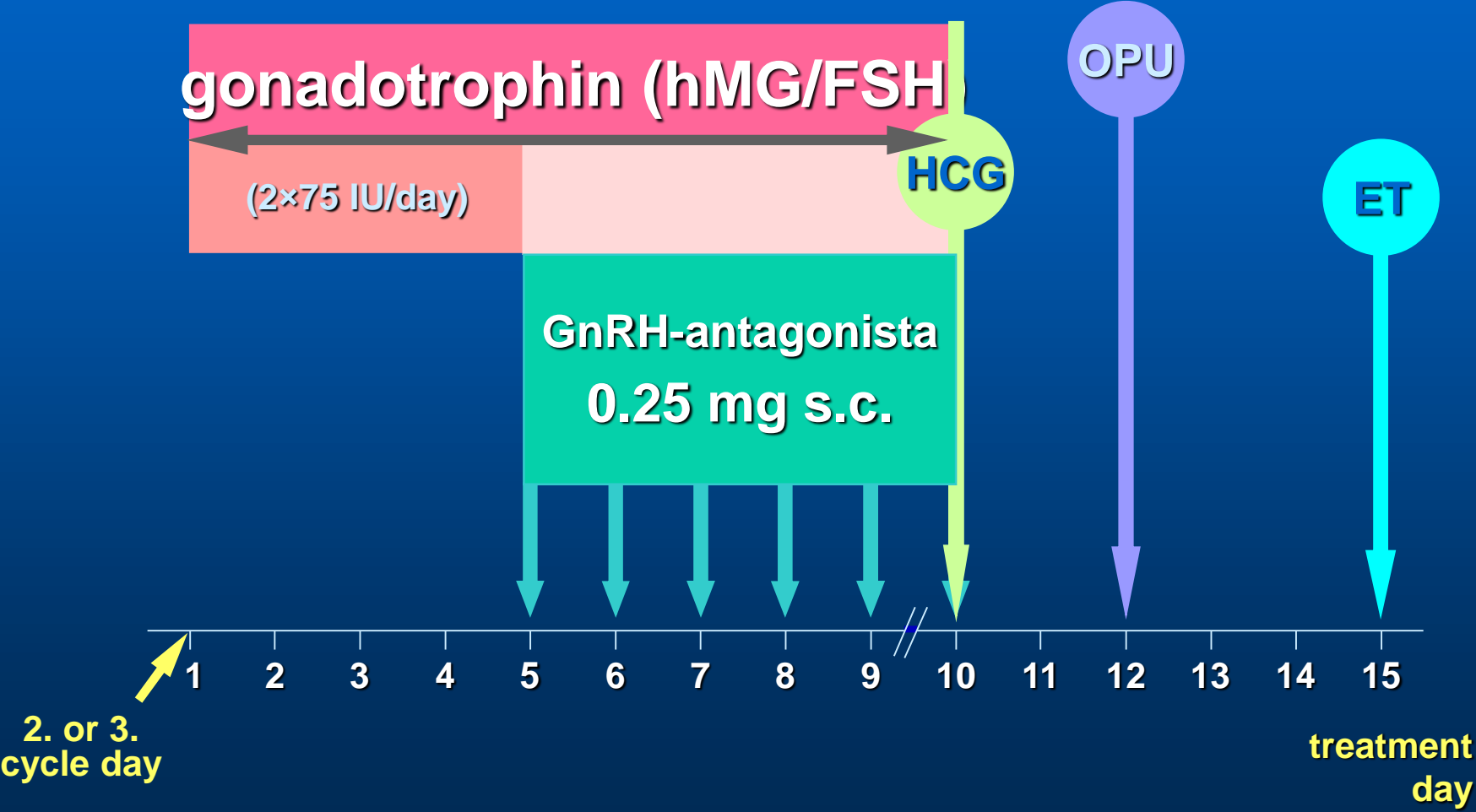


Ovary

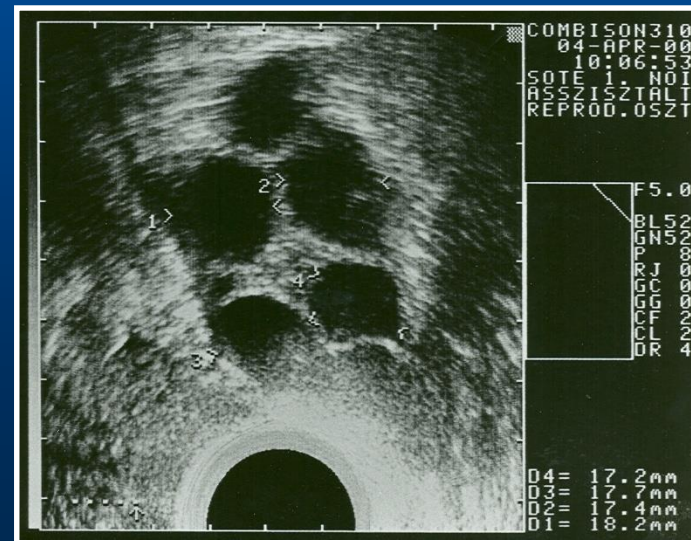
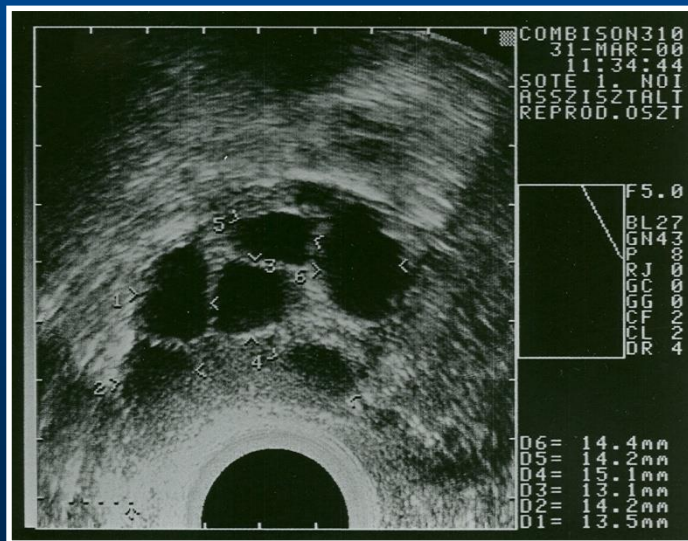
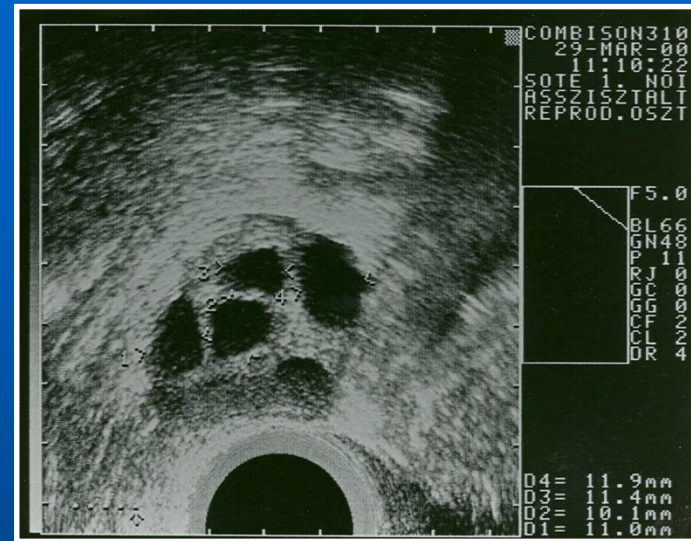
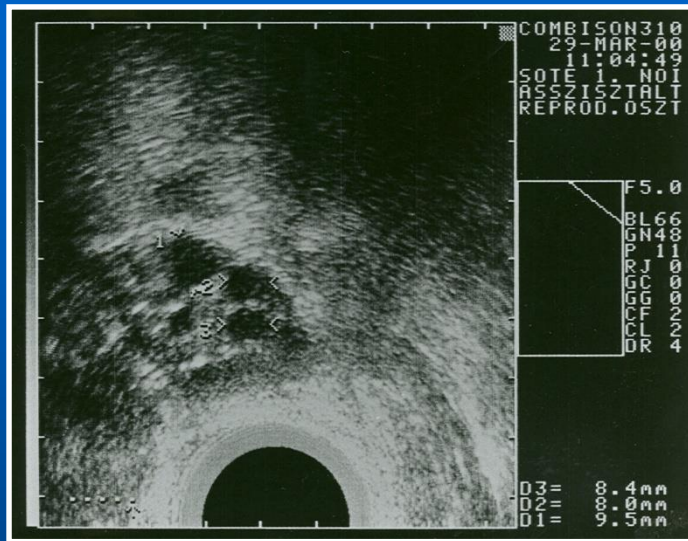
GnRH-antagonist + HMG

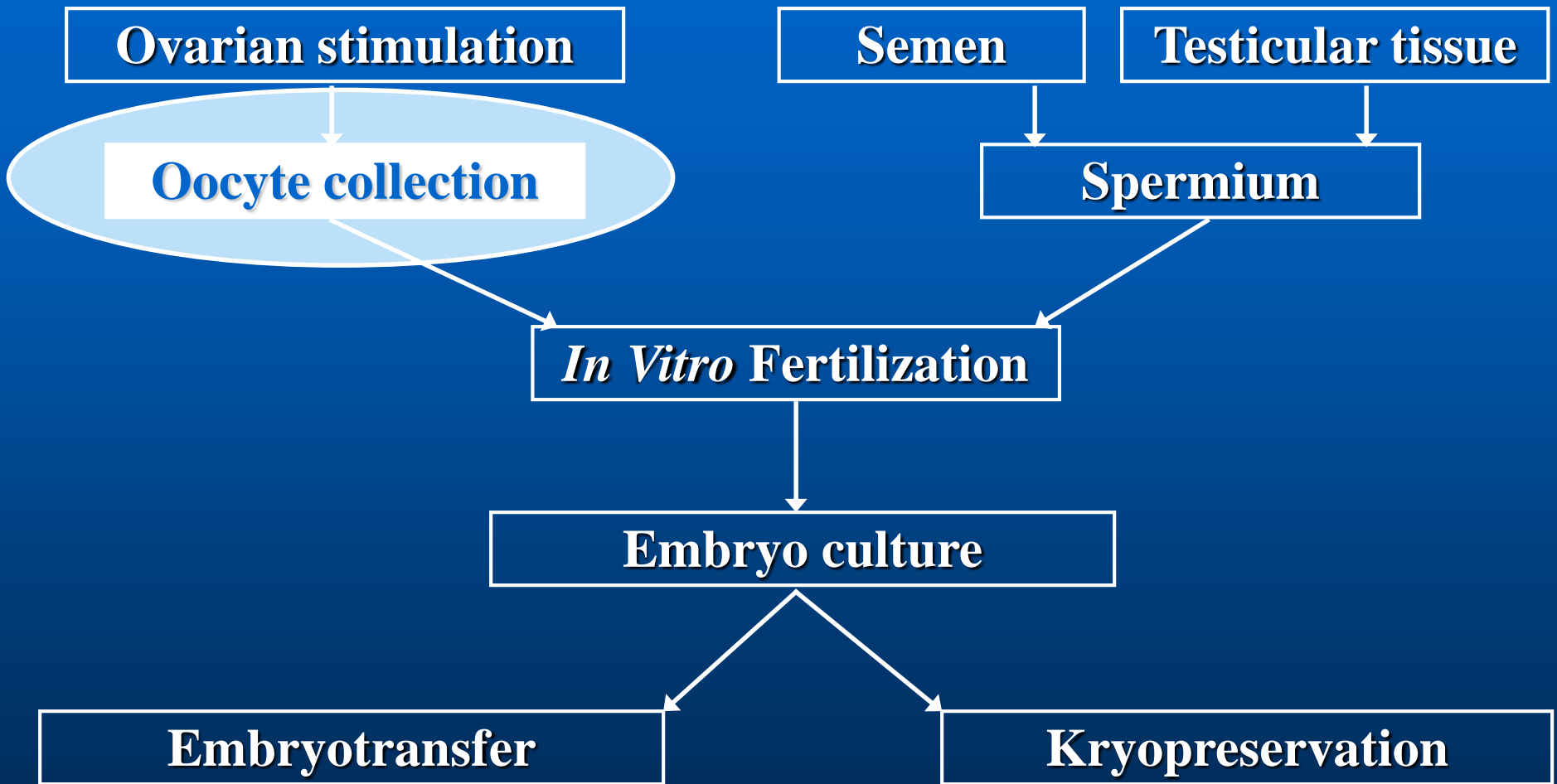


GnRH-antagonist + Gonadotrophin Stimulation

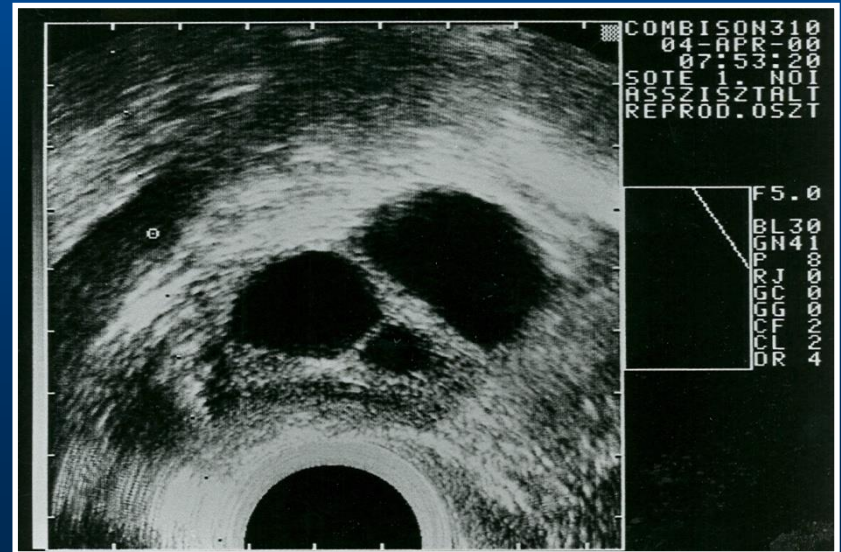
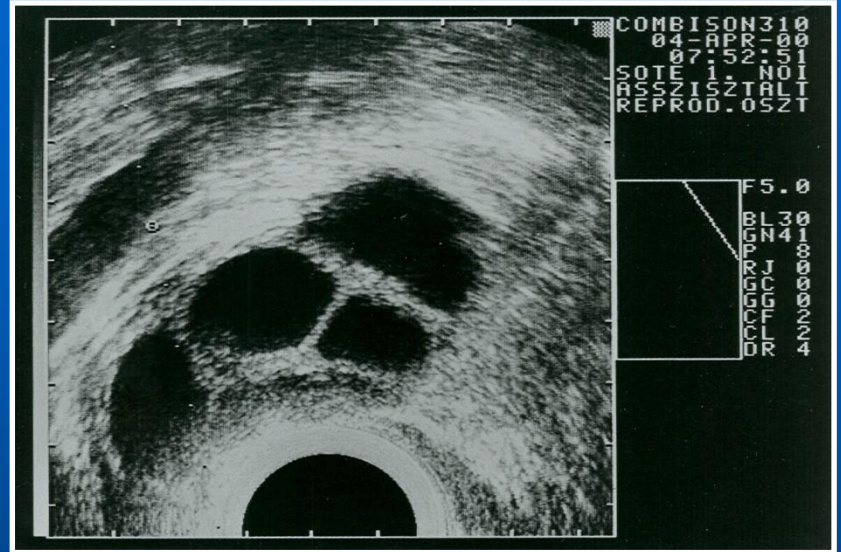
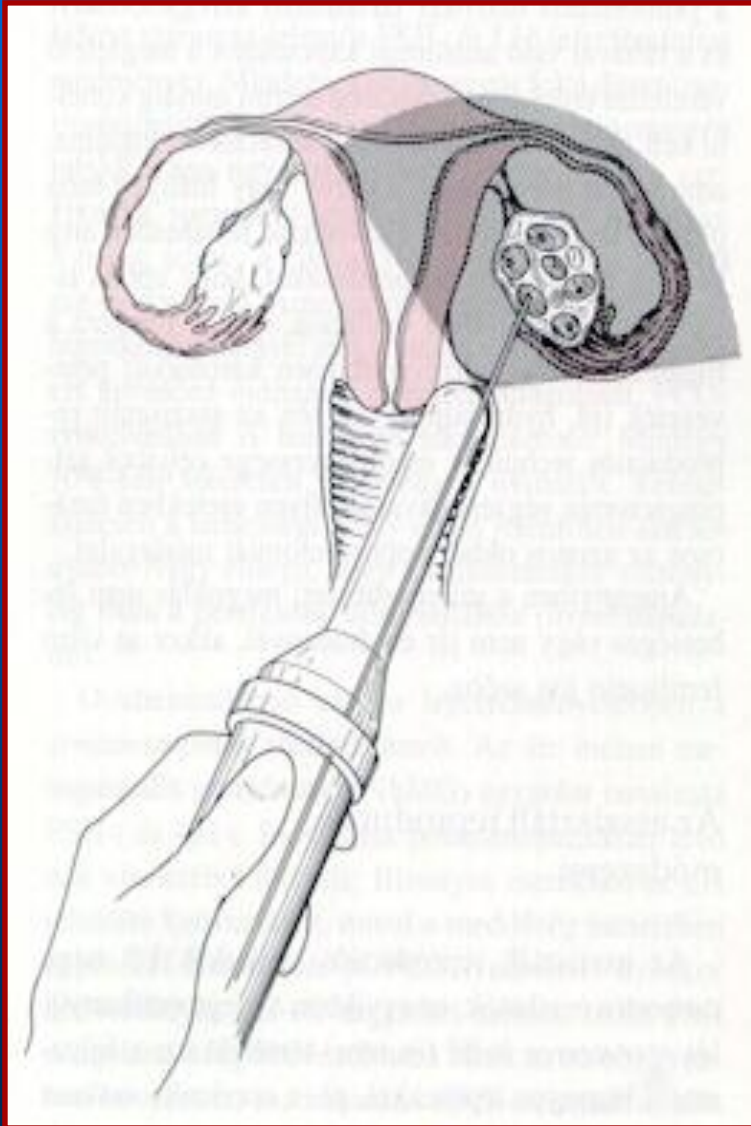


Multiple Follicular Development Transvaginal Ultrasound





Ultrasound Guided Transvaginal Follicle Puncture



128 3E AOK I.NOI ARO
BW

EC4 9ED

2006 05 07

FP3:100

09:40:33

Gynecology

[20] 0.0/8.0

753/P90/TR1.00

102/Gen.



Focus 1

2

Focus

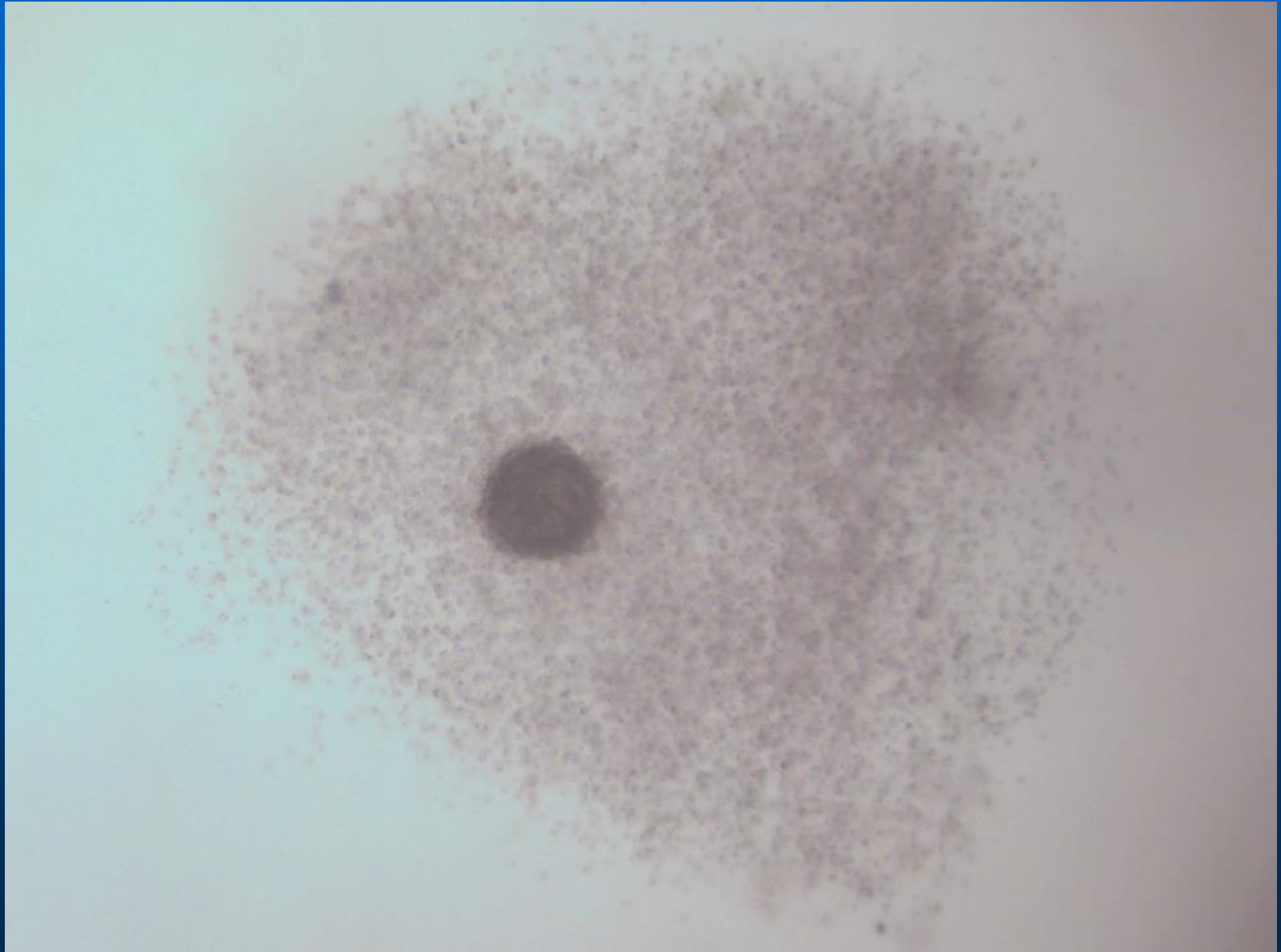
0

HD

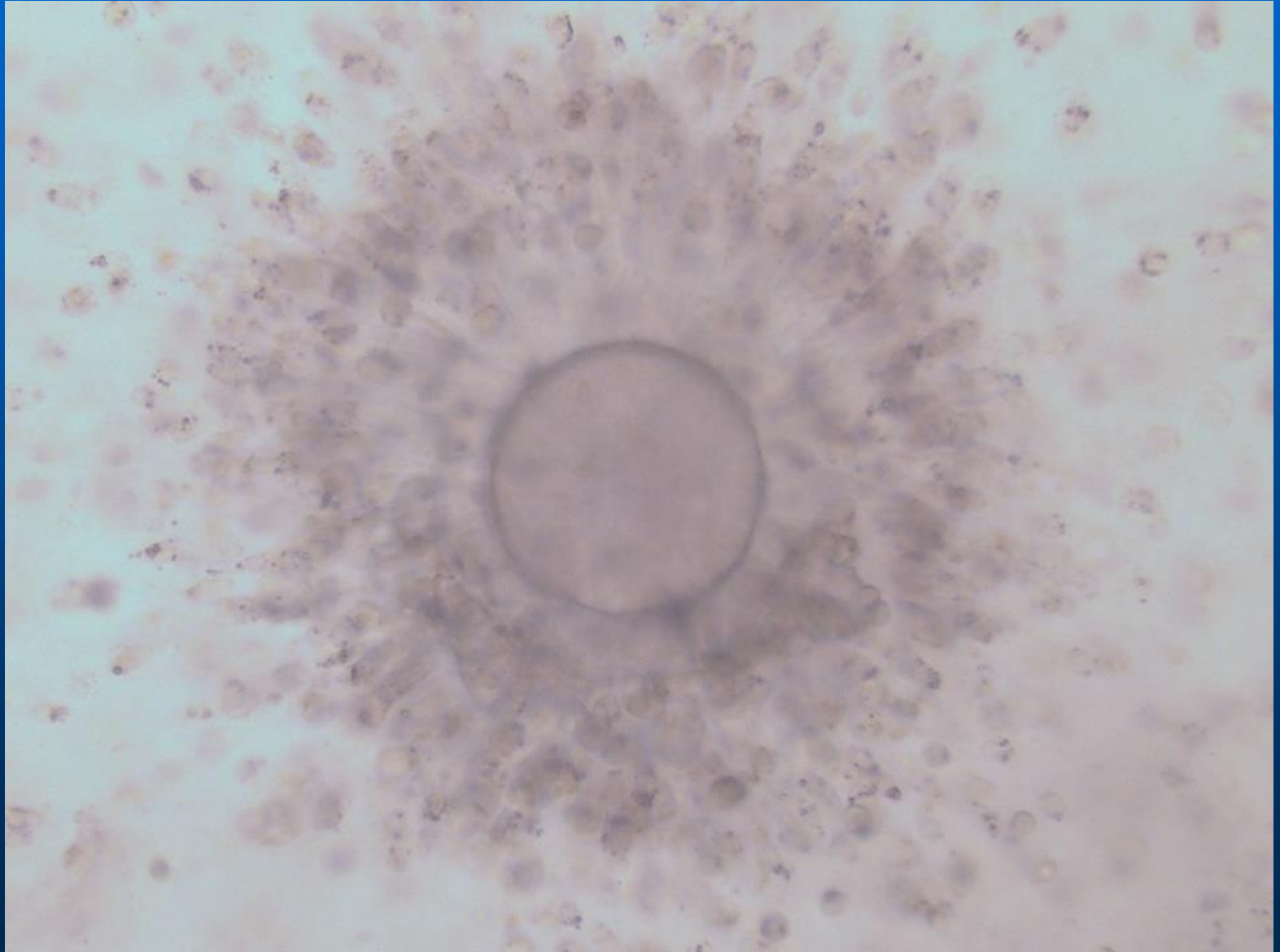
* View Area

View Area

Cumulus-Oocyte Complex I. (COC)



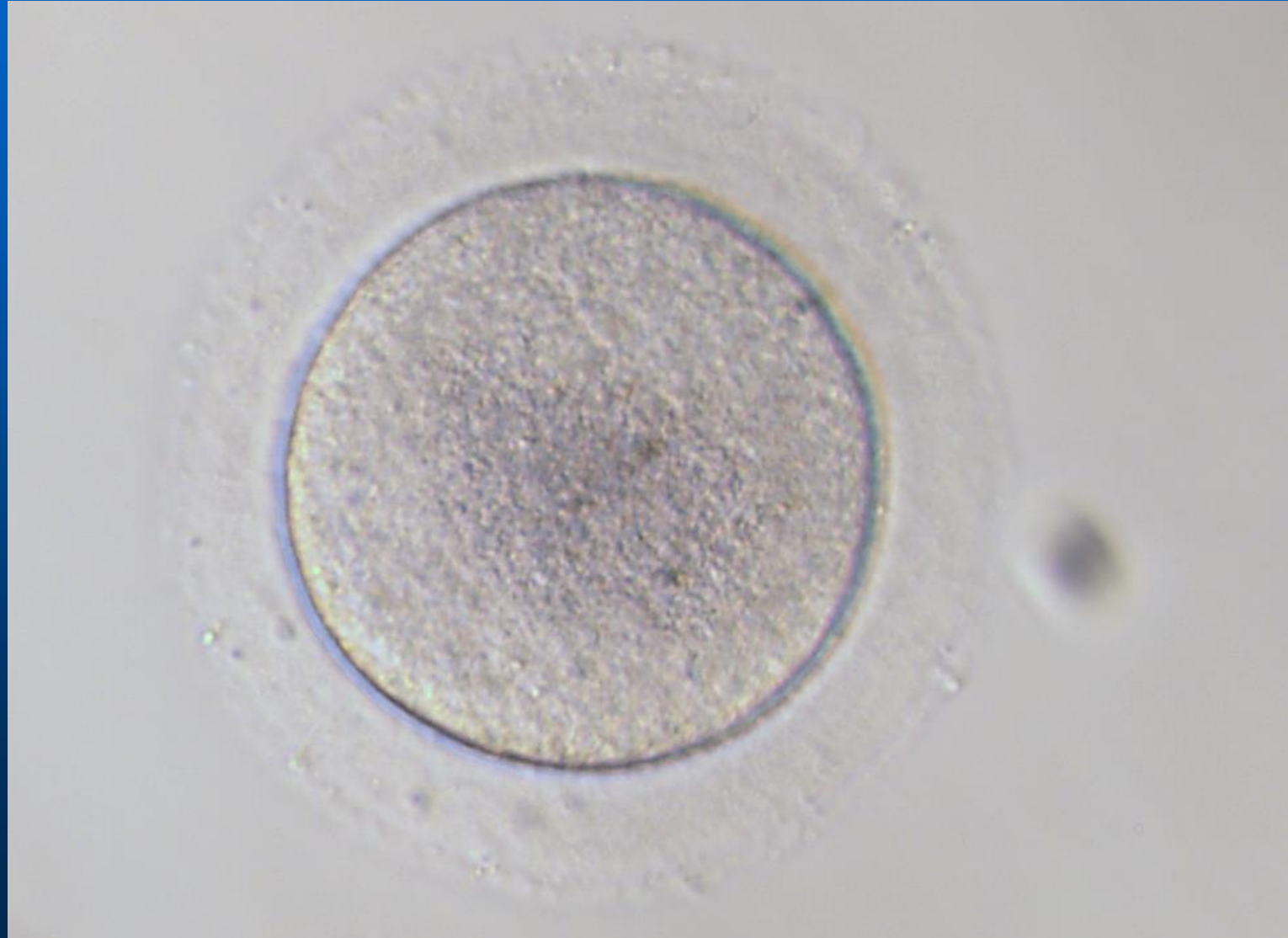
Cumulus-Oocyte Complex II. (COC)



Mature Oocyte Metaphase II. (MII)

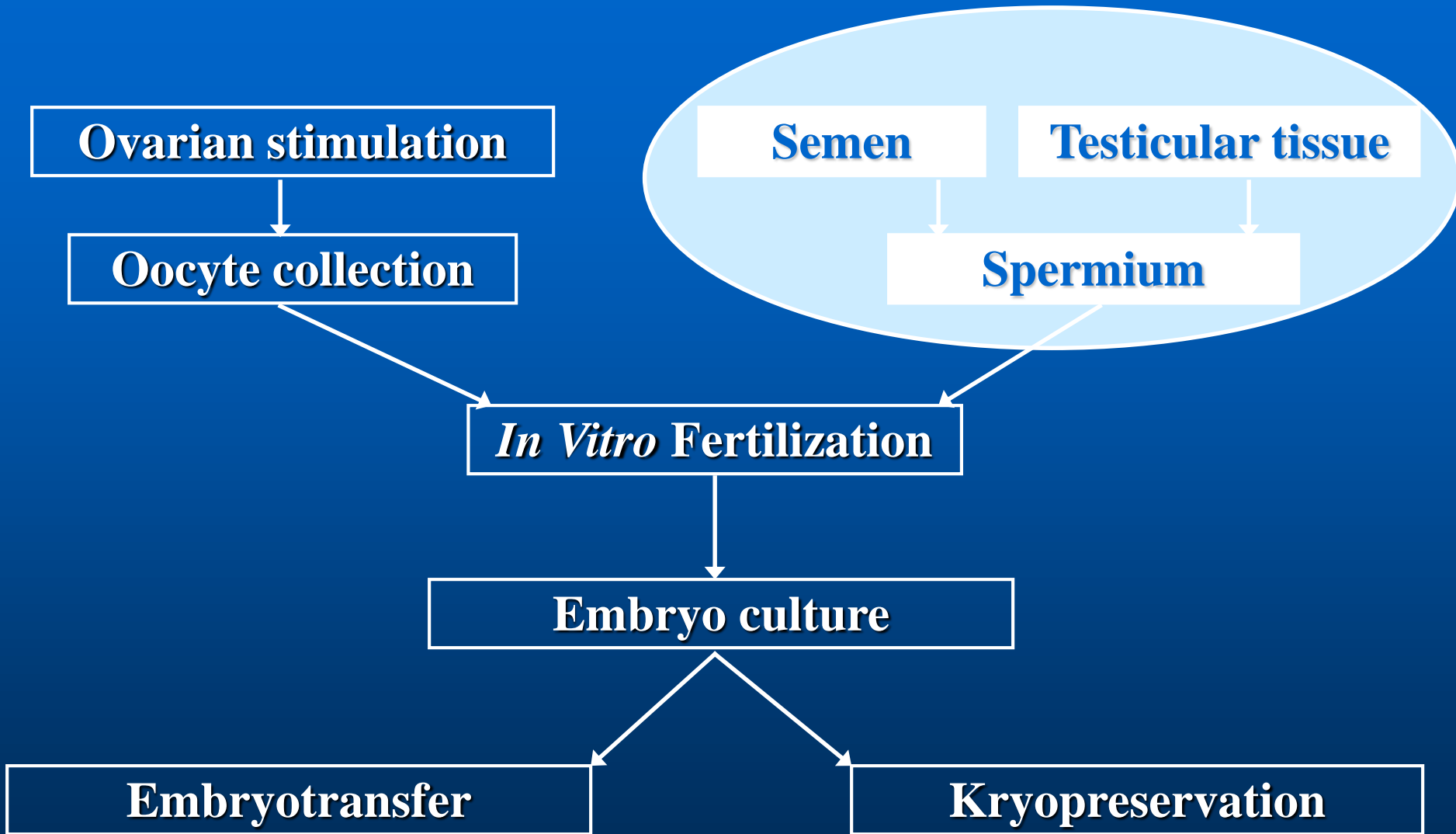


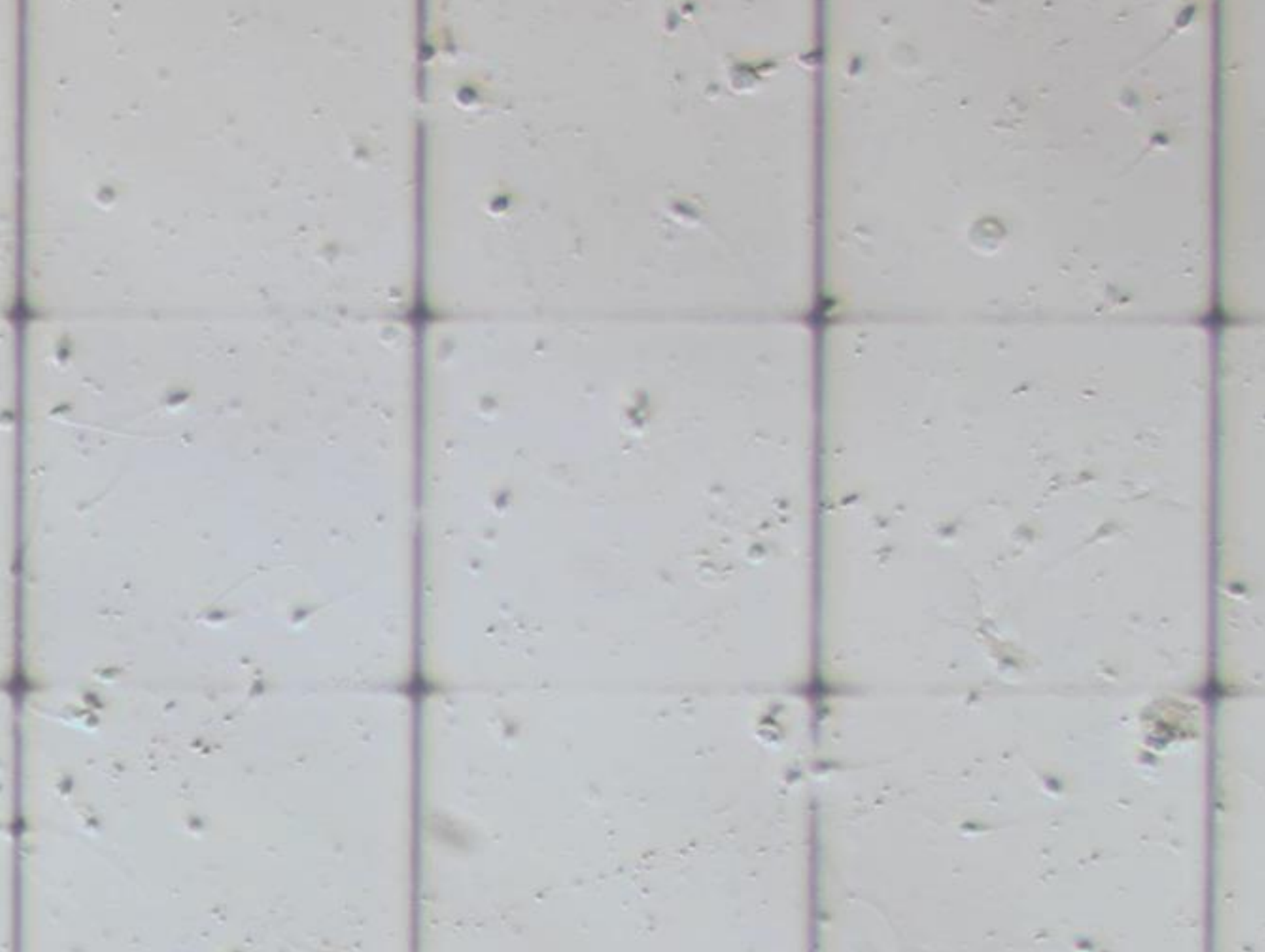
Immature Oocyte Metaphase I. (MI)



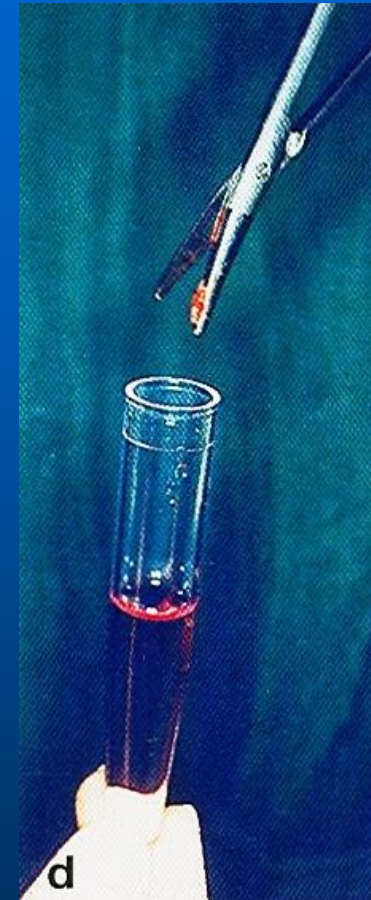
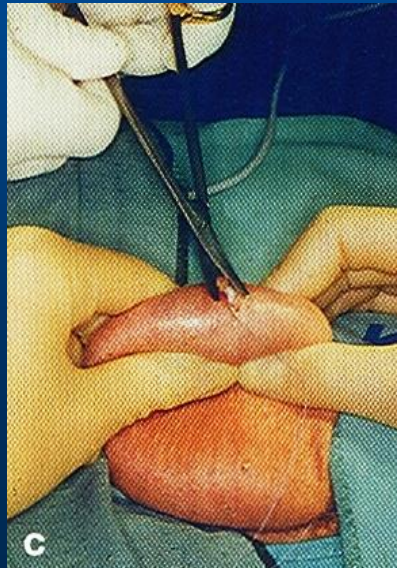
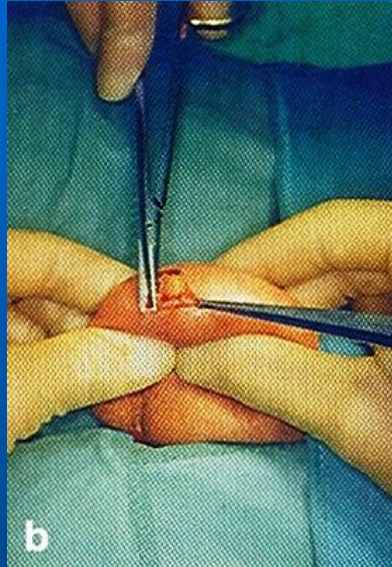
Immature Oocyte Prophase I. (PI)

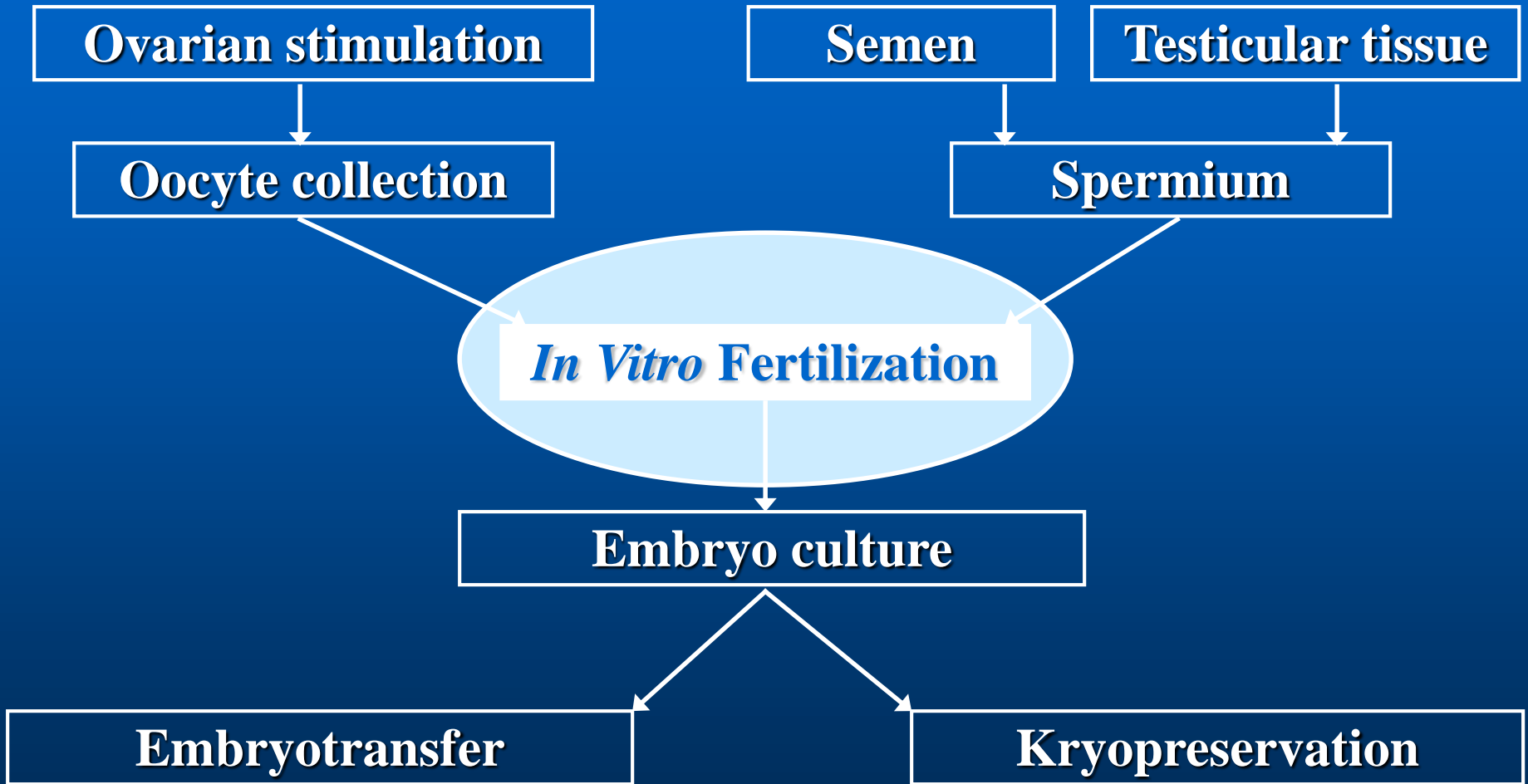




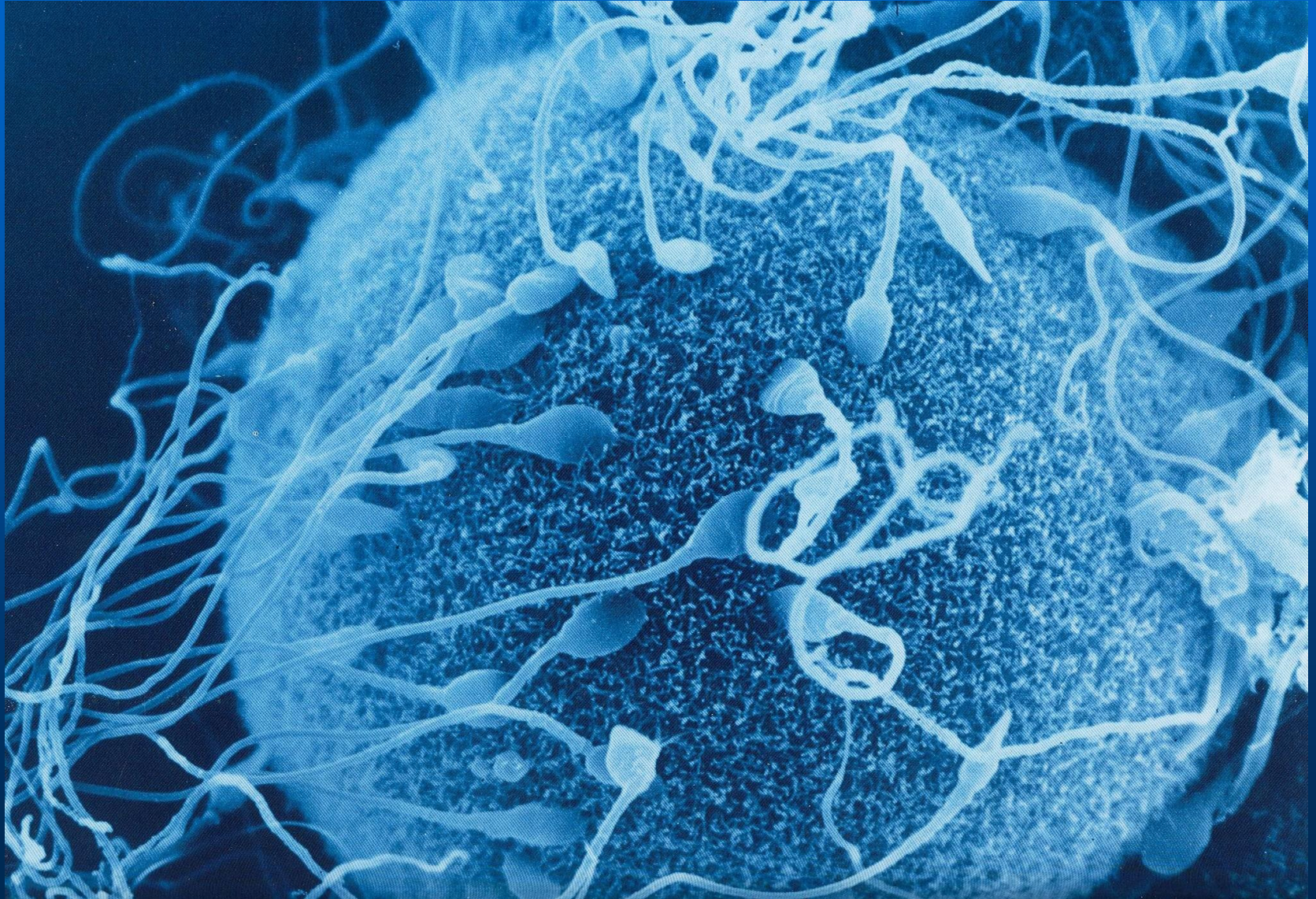


Testicular Sperm Extraction (TESE)

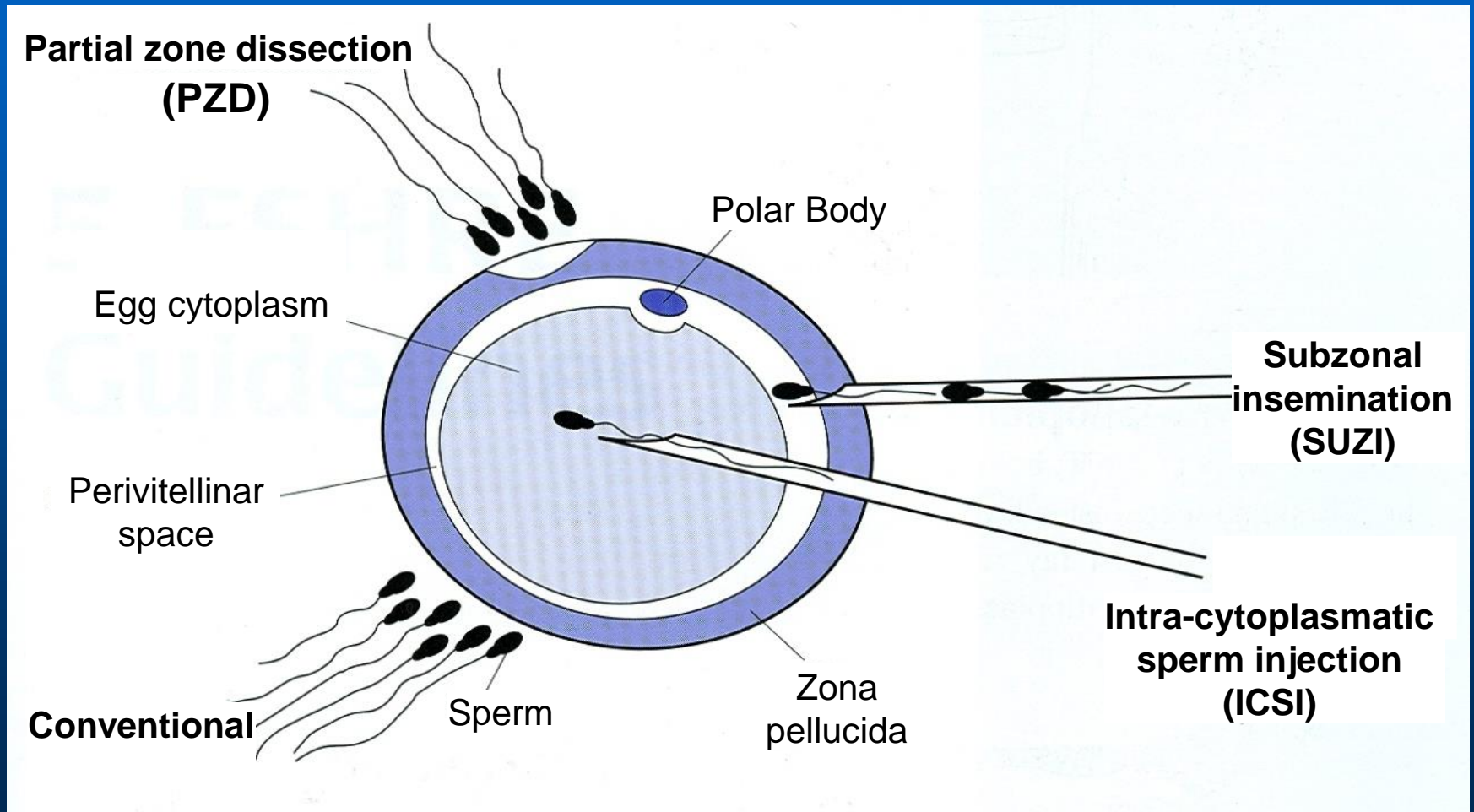




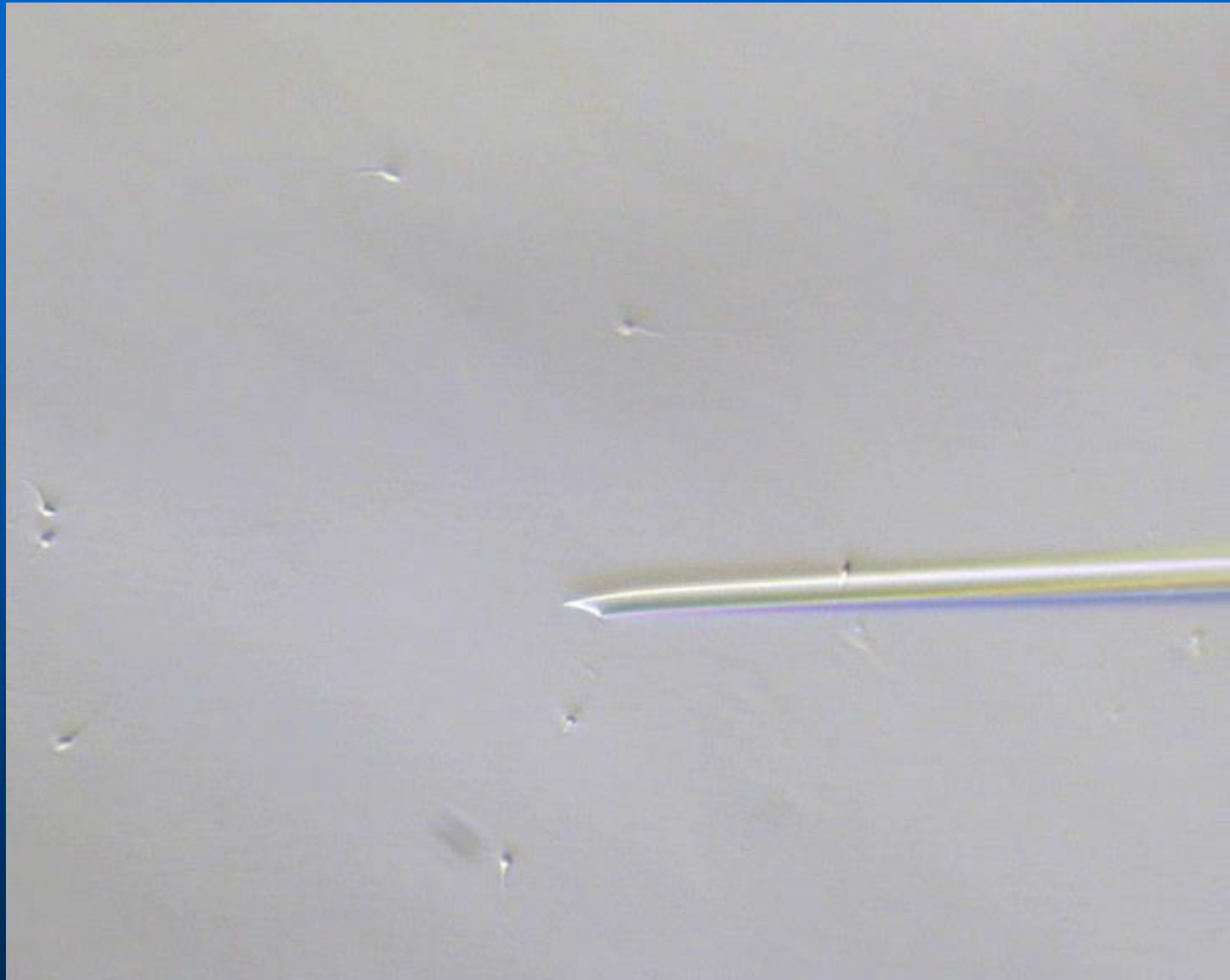
Fertilization

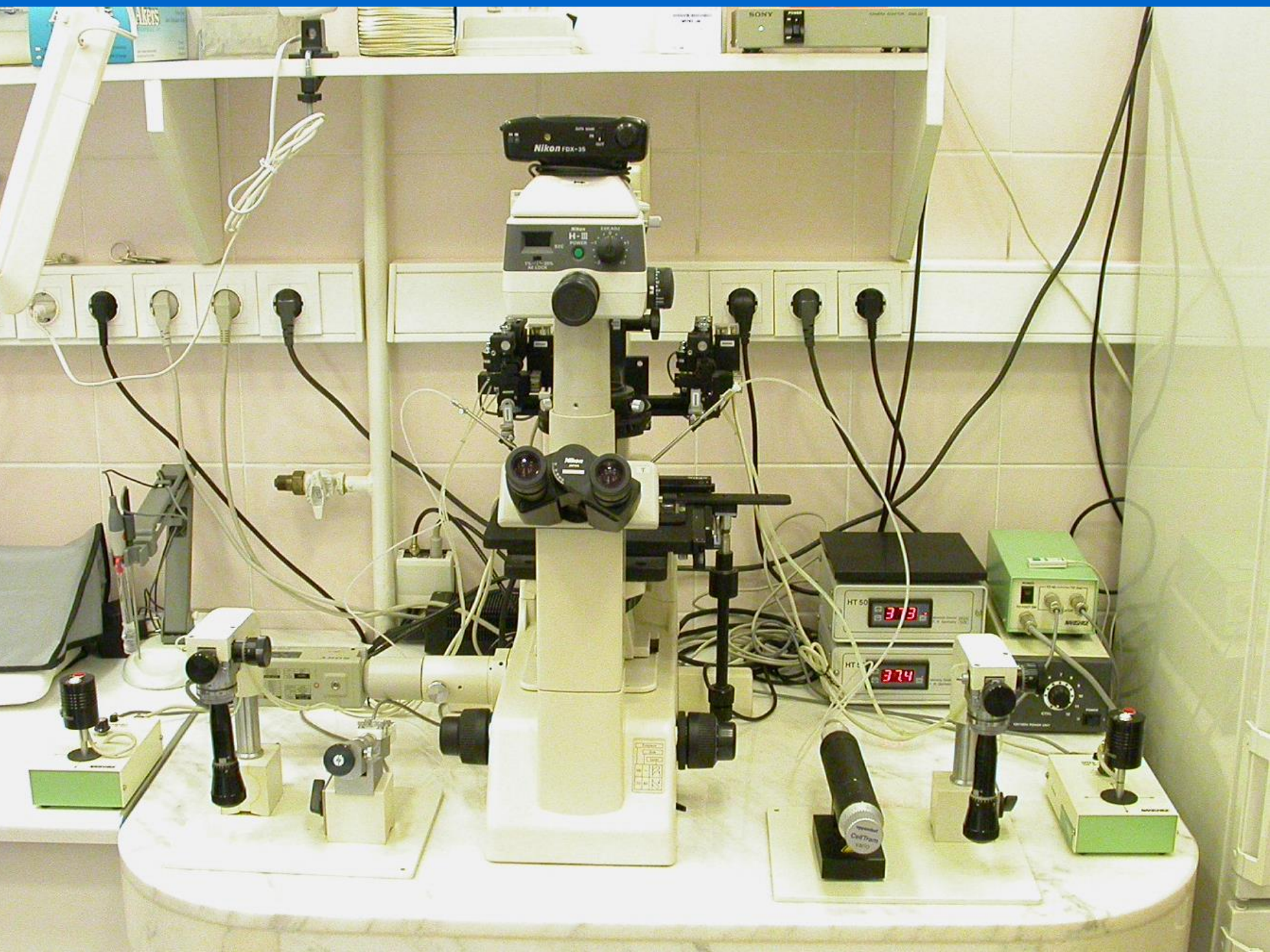


In vitro Fertilization by Micromanipulation Techniques



Intracytoplasmic Sperm Injection (ICSI)







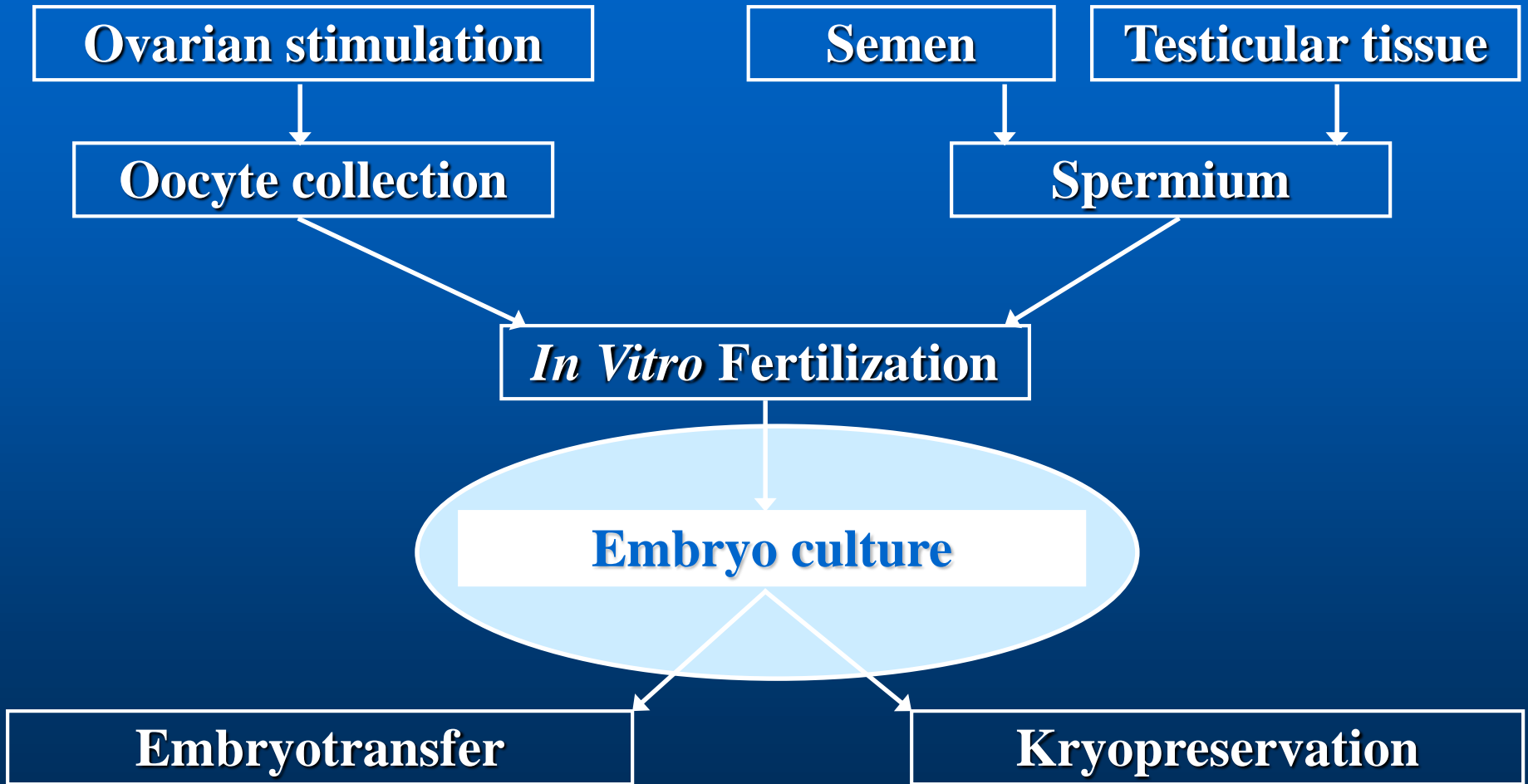
Fertilization Control



2PN



3PN



Embryo Culture

2. day: 2 cell stage

3. day: 8 cell stage

4. day: Morula

5. day: Blastocyst



Embryo Culture

2. day: 4 cell state

3. day: 8 cell state

4. day: morula

5. day: blastocyst



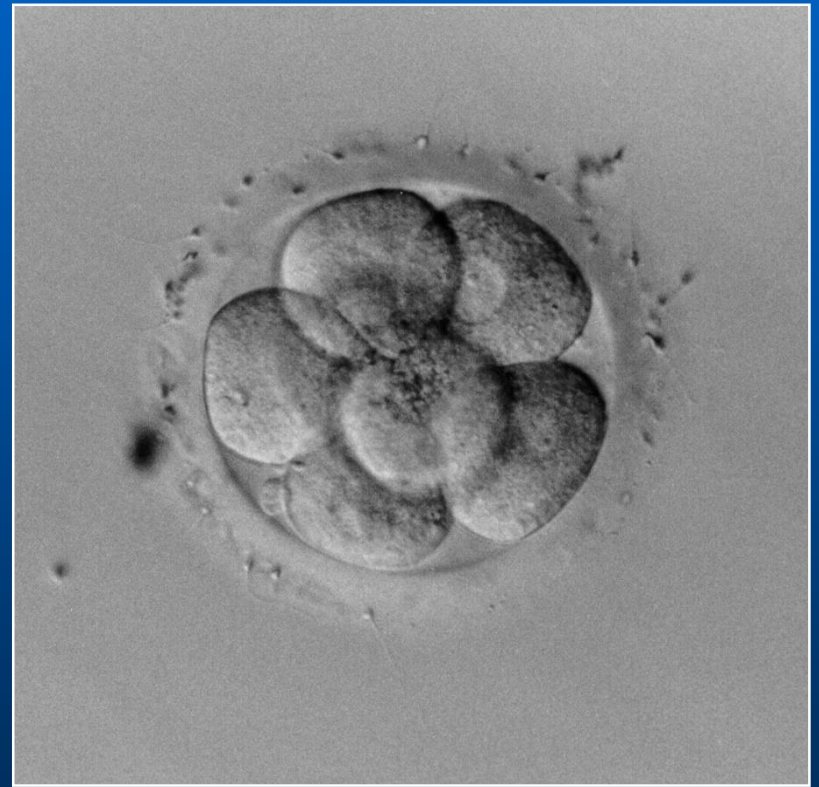
Embryo Culture

2. day: 4 cell state

3. day: 8 cell state

4. day: morula

5. day: blastocyst



Embryo Culture

2. day: 4 cell state

3. day: 8 cell state

4. day: morula

5. day: blastocyst



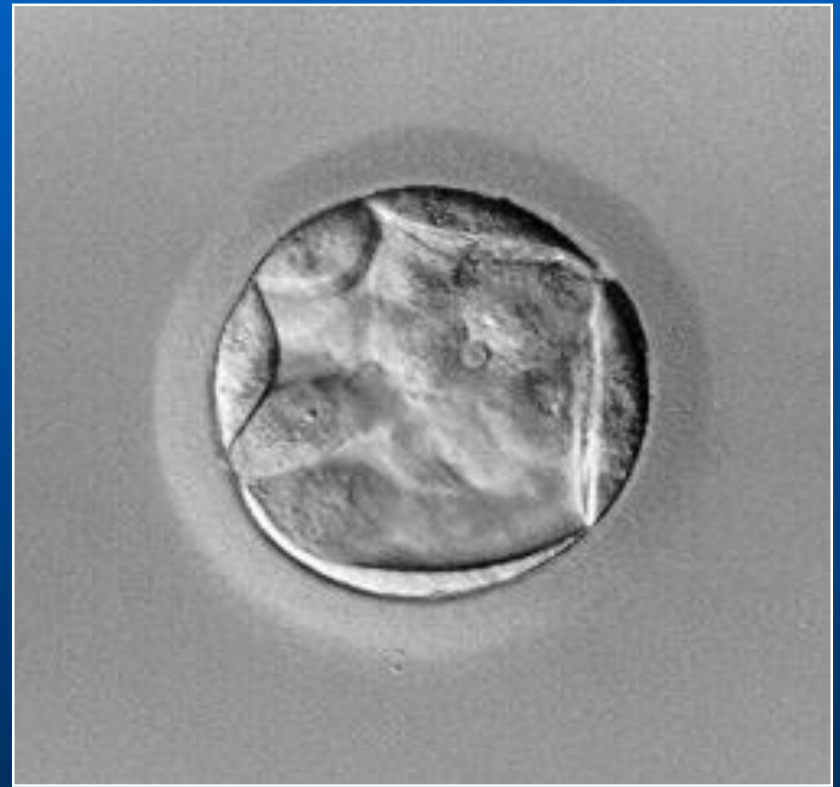
Embryo Culture

2. day: 4 cell state

3. day: 8 cell state

4. day: morula

5. day: blastocyst



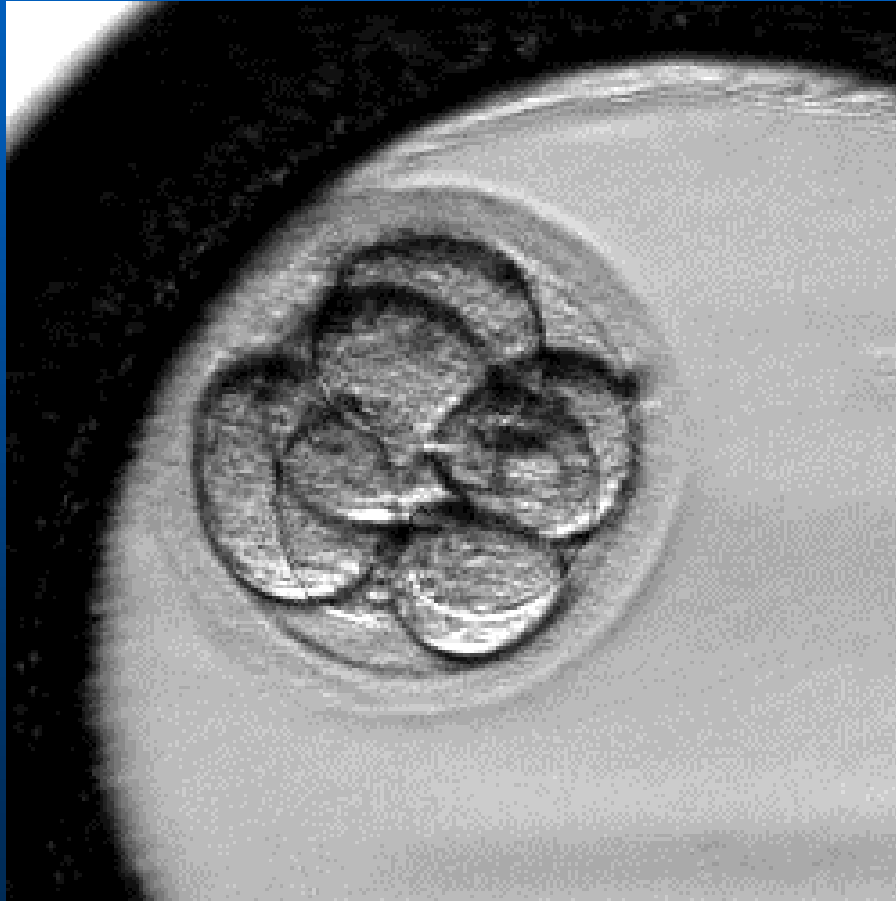
Monitoring of human embryo development by a time-lapse video analysis

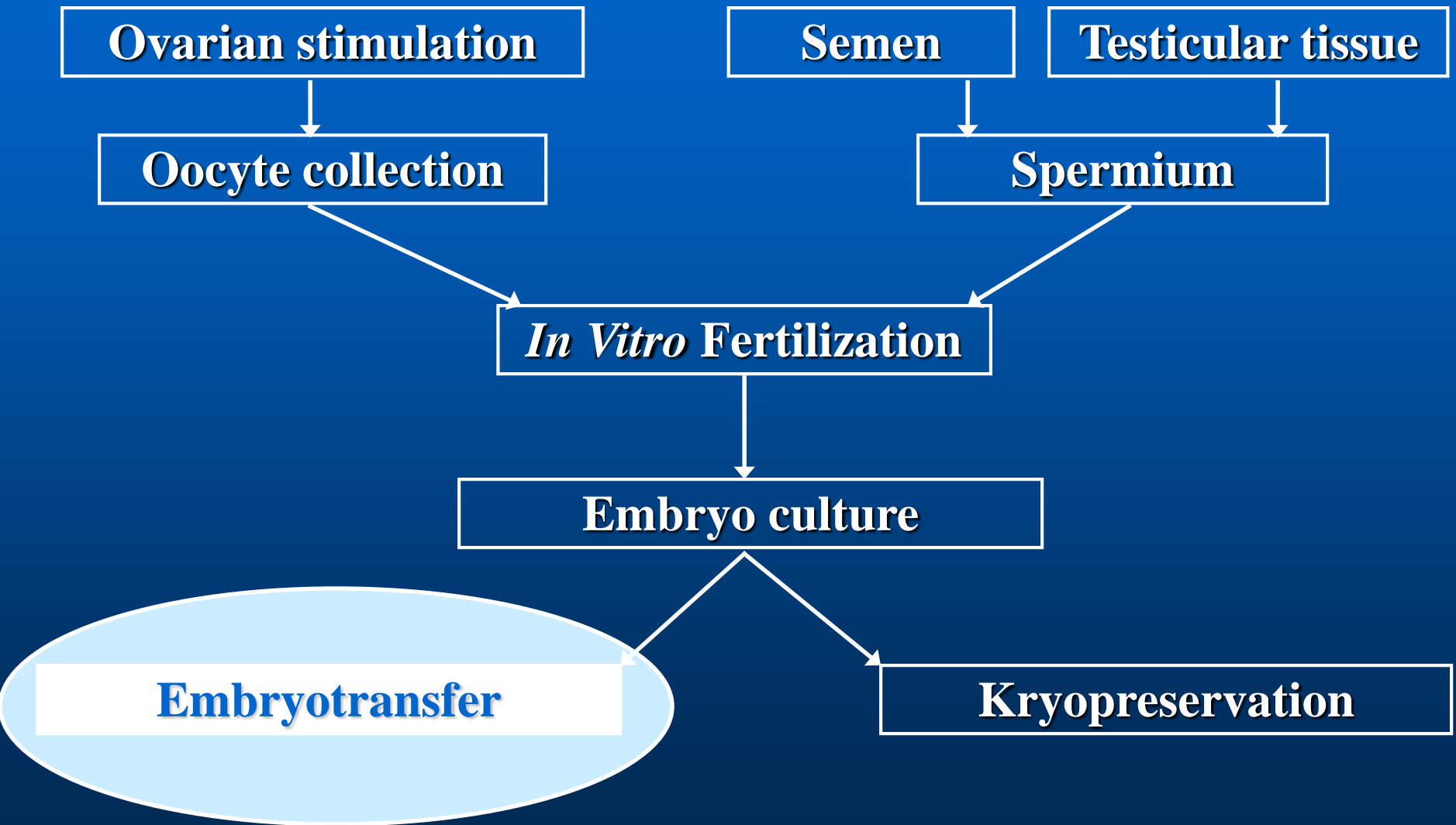


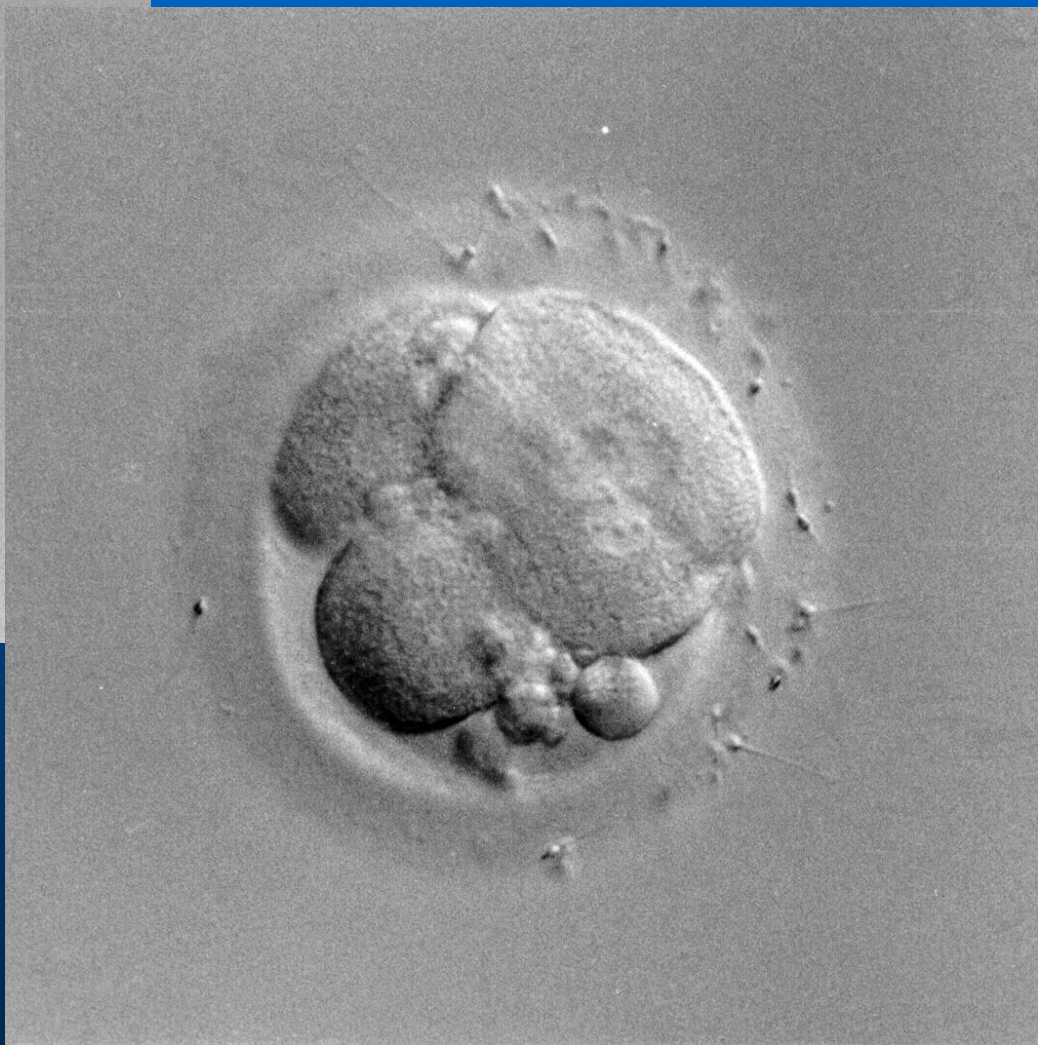
Monitoring of human embryo development by a time-lapse video analysis



Monitoring of human embryo development by a time-lapse video analysis

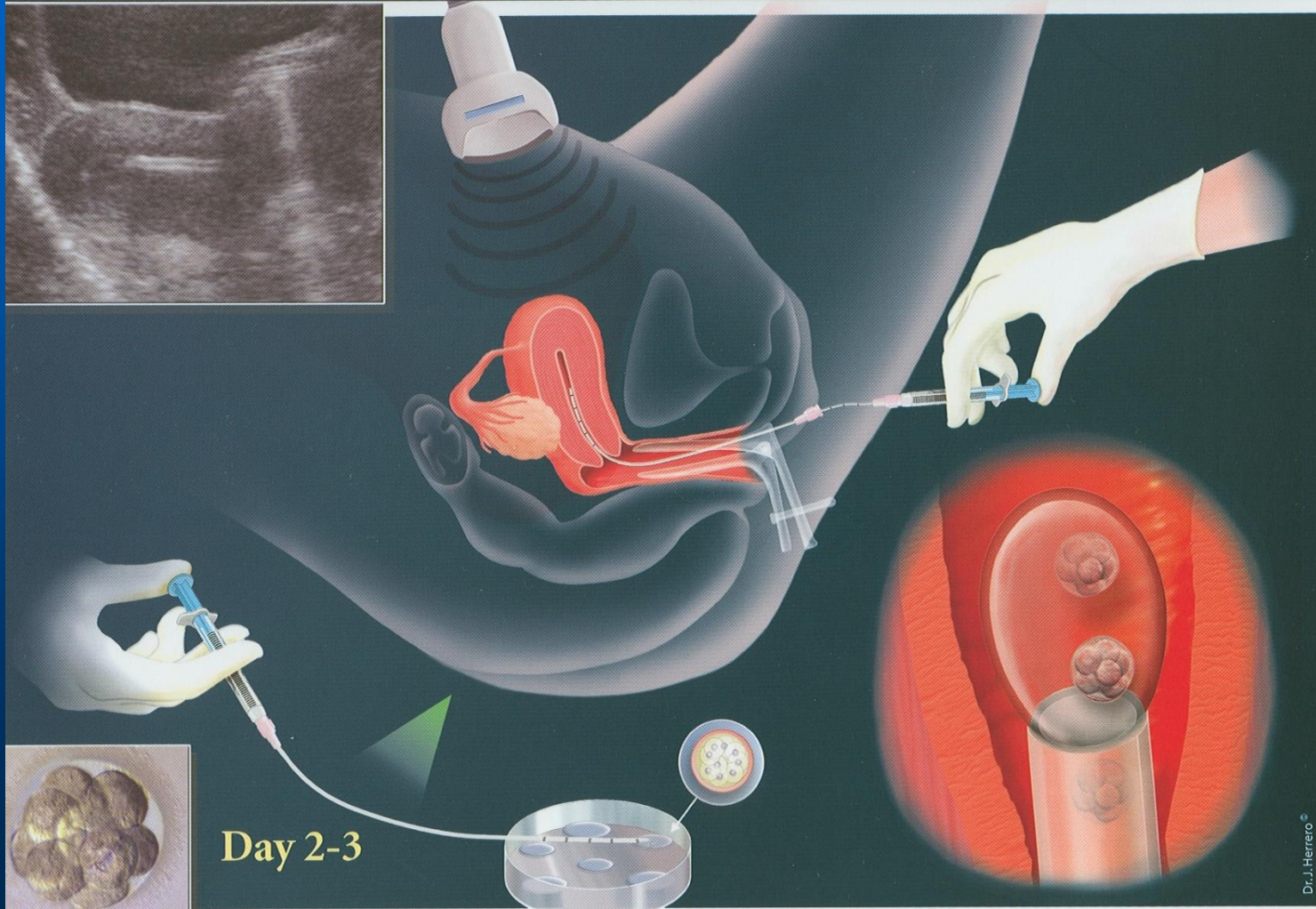






Praeembryotransfer (ET)

Embryo Transfer



Alternative Methods of IVF-ET

GIFT „gamete intrafallopian transfer”

ZIFT „zygote intrafallopian transfer”

TET „tubal embryotransfer”

Micromanipulation Methods in IVF-ET

Assisted fertilisation (PZD, SUZI, ICSI, MESA)

Pronucleus removal

Assisted hatching

Blastomer biopsy for preimplantation genetic
diagnosis (PGD)

Praeimplantation Genetic Diagnosis, PGD)

If parents

have a hereditary disease

don't want to have a sick child

cannot accept arteficial abortion

Indication of Preimplantation Genetic Diagnosis (PGD)

Hereditary (monogenic) disorders

Autosomal dominant

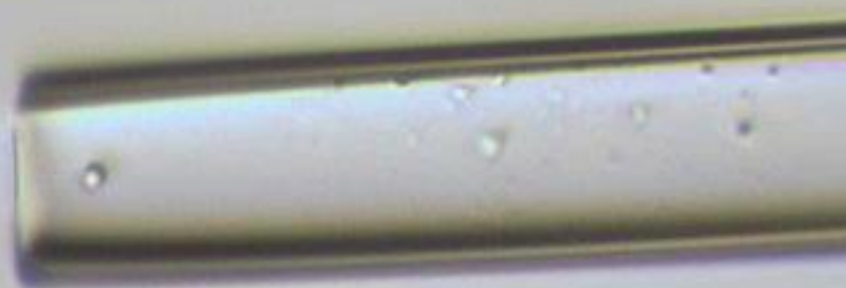
Autosomal recessive

X-chromosome banded recessive

Chromosomal abnormalities

Number (aneuploidy)

Structural (balanced translocations)



Complications of IVF

Complications of ovarian stimulation

Ovarian cyst (10%)

Ovarian hyperstimulation syndrome (OHSS) (5%)

Complications of oocyte pick-up

Pelvic inflammatory disease (1 %)

Vascular injury (1 %)

Intestinal injury (1 %)

Complications of embryotransfer

Extrauterine gravidity (5%)

Spontaneous abortion (20%)

Multiple pregnancy (gemini: 20%, trigemini: 5%)

Symptoms and Stages of Ovarian Hyperstimulation Syndrome (OHSS)

Symptoms	mild	medium	severe
Enlargement of ovary (>12cm)	+	+	+
Abdominal pain	+	+	+
Palpable ovarian cyst		+	+
Meteorism		+	+
Sickness		+	+
Nausea, vomitus		+	+
Diarrhoea		+	+
Ascites		+	+
Hydrothorax			+
Severe haemoconcentration			+
Thromboembolism			+
Pericardial fluid			+
Oligury, anury			+

Complications of IVF

Complications of ovarian stimulation

Ovarian cyst (10%)

Ovarian hyperstimulation syndrome (OHSS) (5%)

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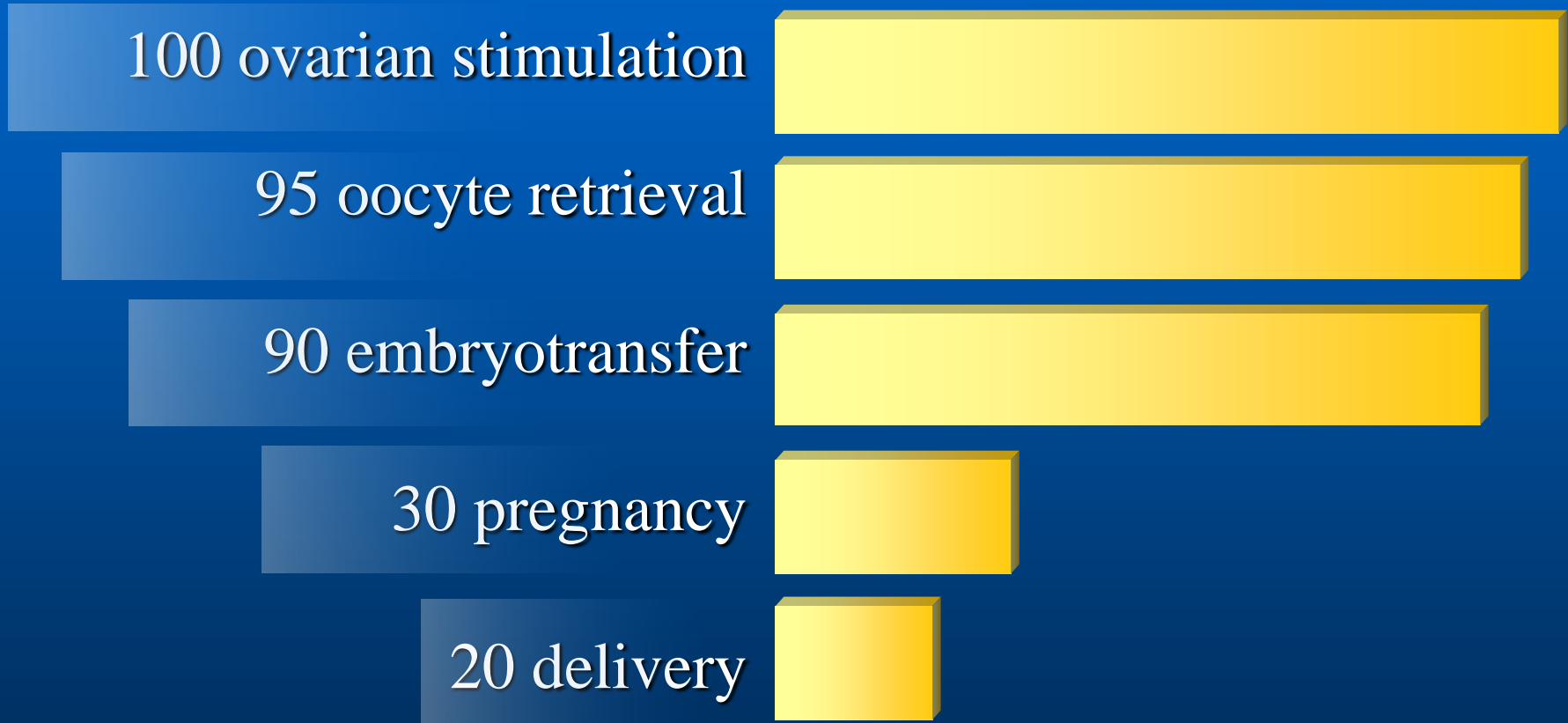
Complications of embryotransfer

Extrauterine gravidity (5%)

Spontaneous abortion (20%)

Multiple pregnancy (gemini: 20%, trigemini: 5%)

Success Rate of IVF Treatment



IVF-ET Treatment With Third (Fourth) Participant

Oocyte donation

Sperm donation

Embryo donation

Surrogacy

Indications of Oocyte Donation

Premature ovarian failure

After ovariectomy

After chemotherapy / irradiation

Hereditary disease

Abnormal oocytes

Indications of Surrogacy

Inability to carry a pregnancy to term

no uterus

congenital (malformation)

occupied (operation)

abnormal uterine cavity

congenital (malformation)

occupied (adhaesions after inflammation)

Pregnancy is contraindicated due to severe disease

(severe diabetes, hepatic disease, hypertension)

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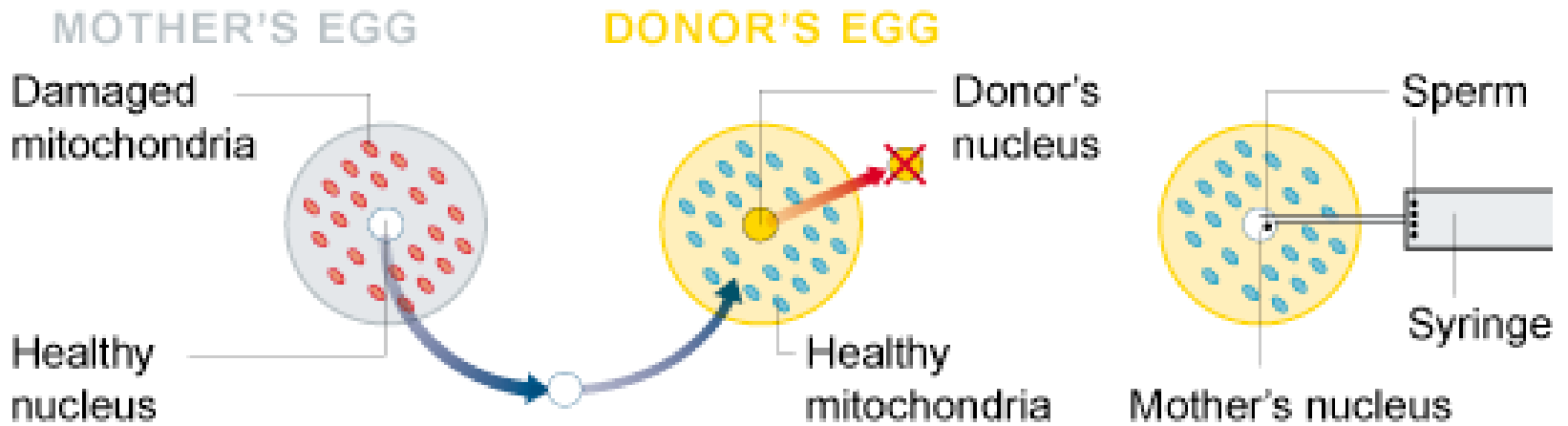
Exclusive: World's first baby born with new "3 parent" technique



Blackout Concepts/Alamy

By Jessica Hamzelou

CREATING A THREE-PARENT FAMILY



1 Healthy nucleus is extracted from mother's defective egg

2 Nucleus removed from healthy donor egg and replaced with mother's nucleus

3 Egg carrying genetic material of two women fertilised by male sperm and implanted into mother



Cloning

Genetically identical

identical twins (natural clones)

embryo splitting

nuclear transfer

embryonal cells

fetal cells

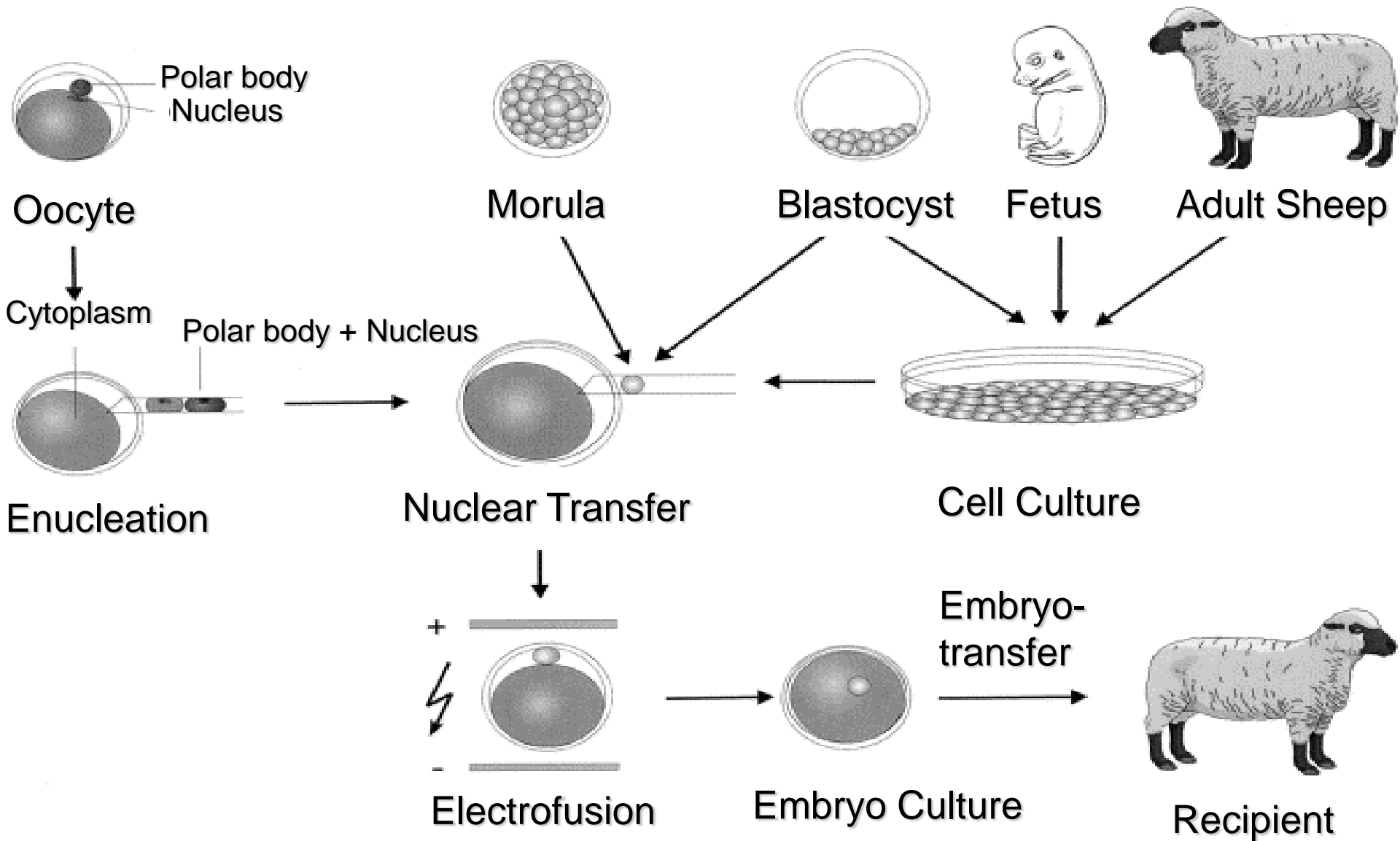
adult cells

Purpose:

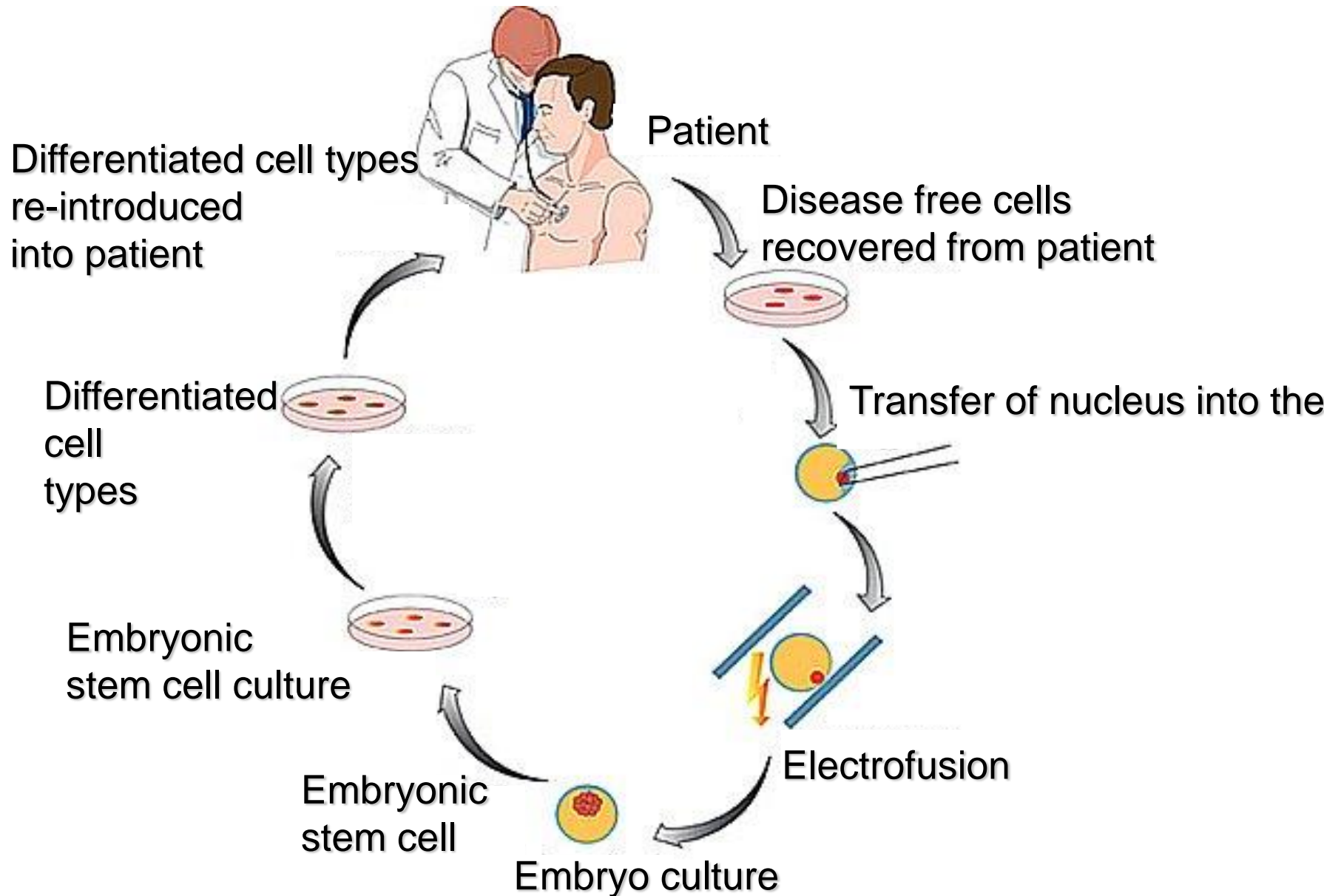
therapy

reproduction

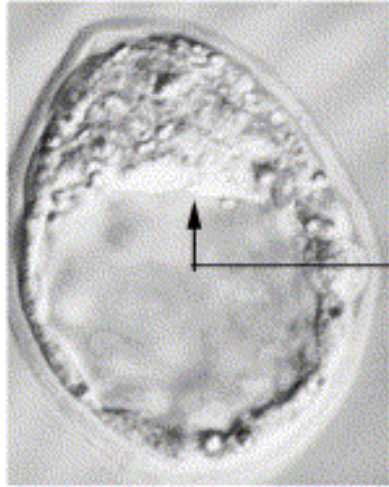
Reproductive Cloning



Therapeutic Cloning I.



Therapeutic Cloning I.



Blastocyst



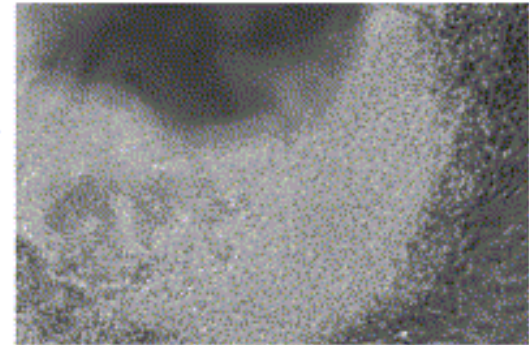
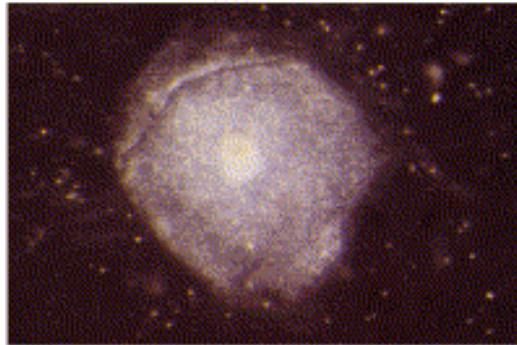
Embryonic stem cell



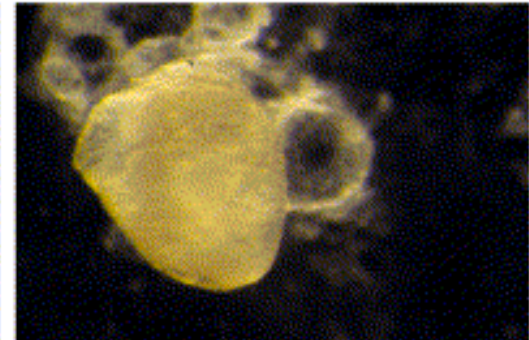
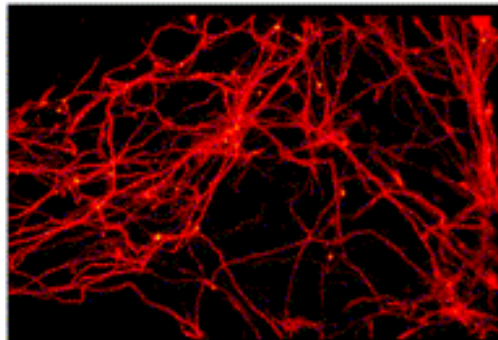
Stem cell isolation



Undifferentiated stem cells



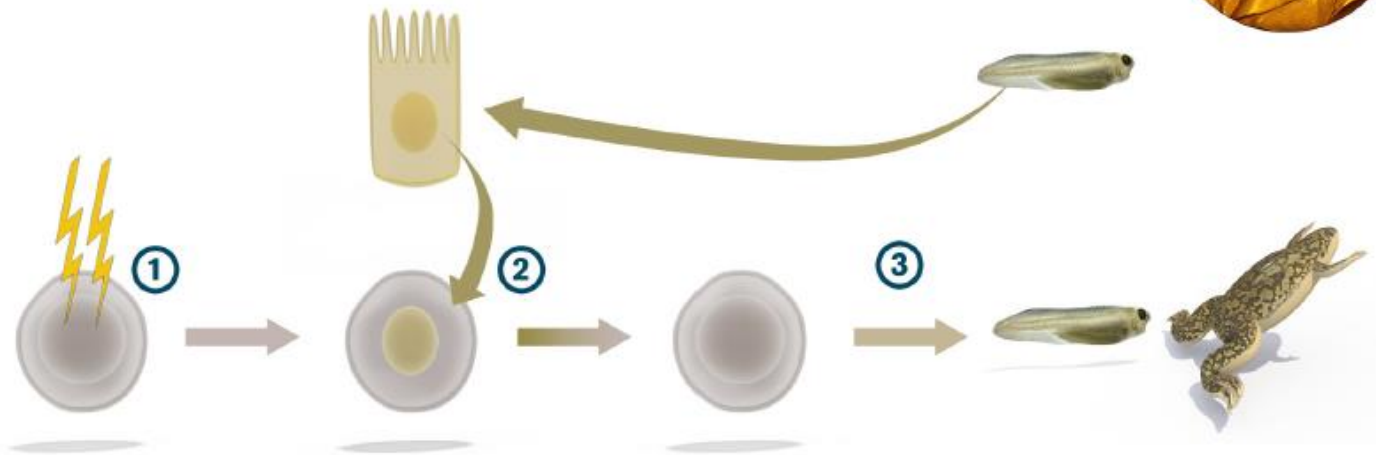
Differentiated stem cells



The Nobel Prize in Physiology or Medicine 2012

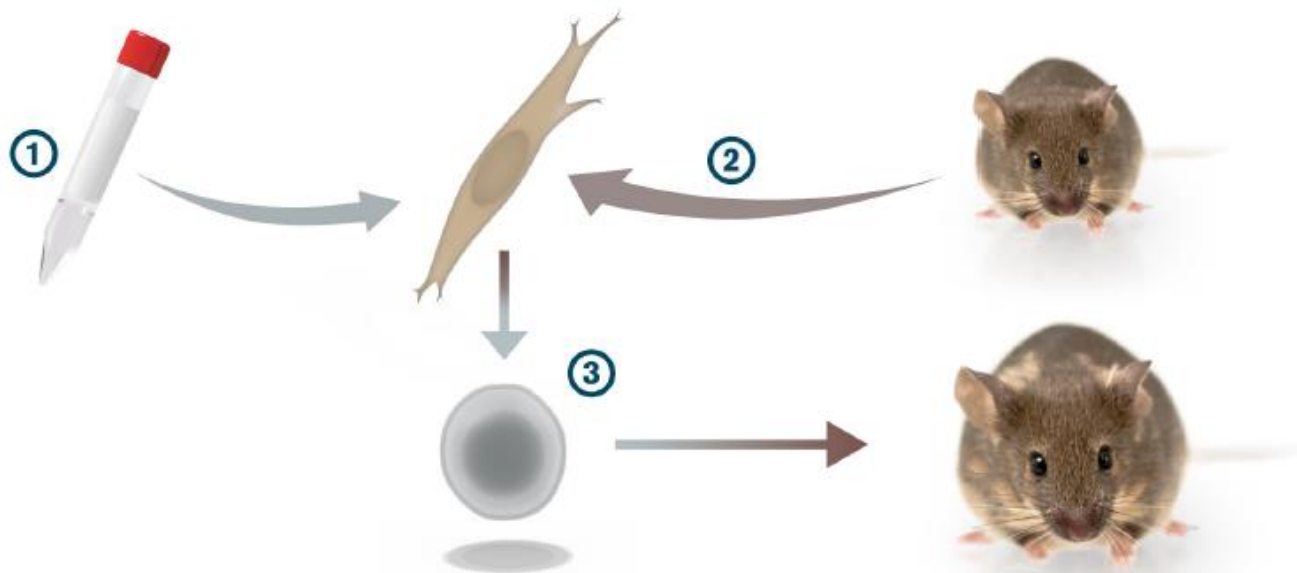


John B. Gurdon



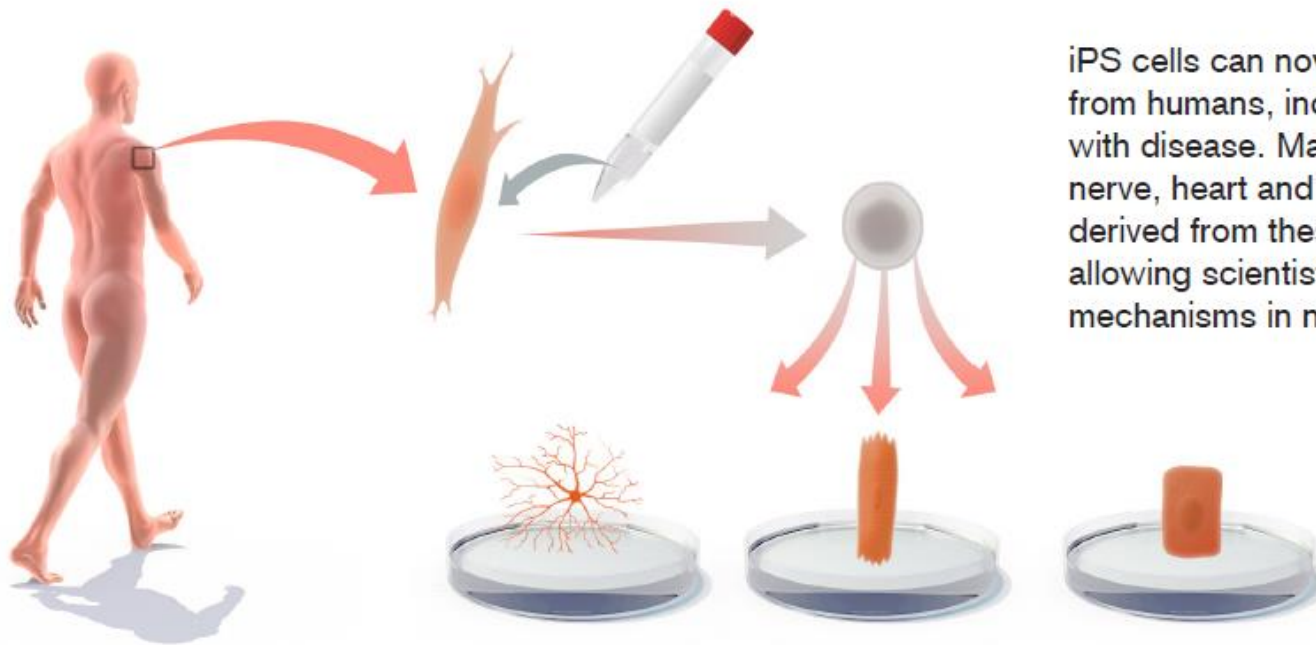
John B. Gurdon eliminated the nucleus of a frog egg cell (1) and replaced it with the nucleus from a specialised cell taken from a tadpole (2). The modified egg developed into a normal tadpole (3). Subsequent nuclear transfer experiments have generated cloned mammals (4).





Shinya Yamanaka

Shinya Yamanaka studied genes that are important for stem cell function. When he transferred four such genes (1) into cells taken from the skin (2), they were reprogrammed into pluripotent stem cells (3) that could develop into all cell types of an adult mouse. He named these cells induced pluripotent stem (iPS) cells.



iPS cells can now be generated from humans, including patients with disease. Mature cells including nerve, heart and liver cells can be derived from these iPS cells, thereby allowing scientists to study disease mechanisms in new ways.

Thank You For Your Attention

