Università degli studi di Ferrara

INFERTILITA' E PROCREAZIONE MEDICALMENTE ASSISTITA

Corso di Ginecologia e Ostetricia
29/04/2016

EPIDEMIOLOGY OF INFERTILITY
FACTORS AFFECTING INFERTILITY

Requirements for conception

Production of healthy egg and sperm

Unblocked tubes that allow sperm to reach the egg

The sperms ability to penetrate and fertilize the egg

Implantation of the embryo into the uterus

Finally a healthy pregnancy

Definitions

Fecundability

The probability of conceiving in a single menstrual cycle

Time to Pregnancy (TTP)

The length of time in months that takes a couple to concieve

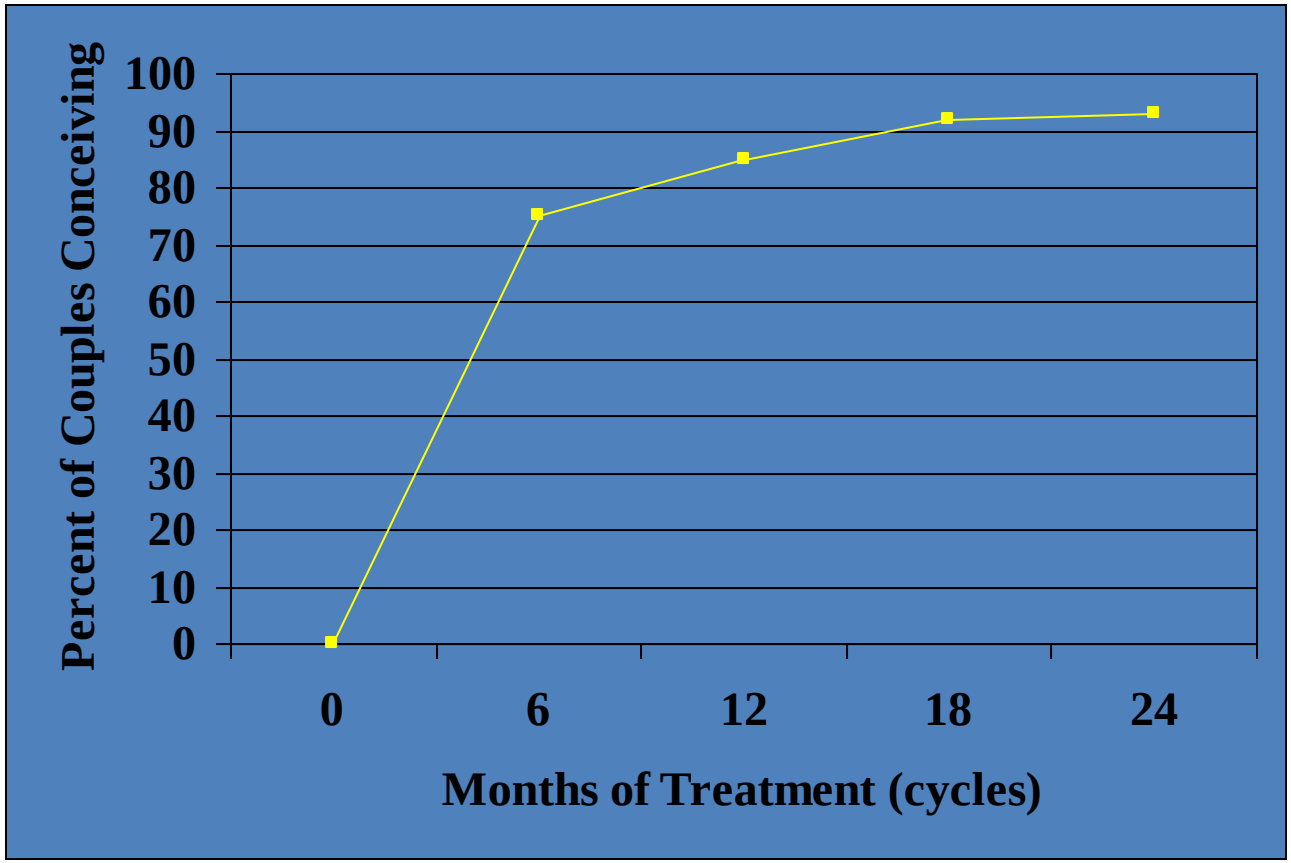
Normal Fertility

Monthly conception rate: 20-25% in normal fertile couples

The large majority (80 to 90 percent) of apparently normal couples will conceive within the first year of attempted conception

Normal Fertility

After 24 months of trying to become pregnant, 95% of couples will have conceived.



Infertility

The inability to conceive following regular unprotected sexual intercourse

1 year (age < 35) or 6 months (age >35)

Affects 12-18% of reproductive couples

6.1 million couples

Infertility

Primary infertility

a couple that has never conceived

Secondary infertility

infertility that occurs after previous pregnancy regardless of outcome

ICMART - WHO revised glossary of ART terminology, 2009 Fertil Steril 2009

Infertility - Epidemiology

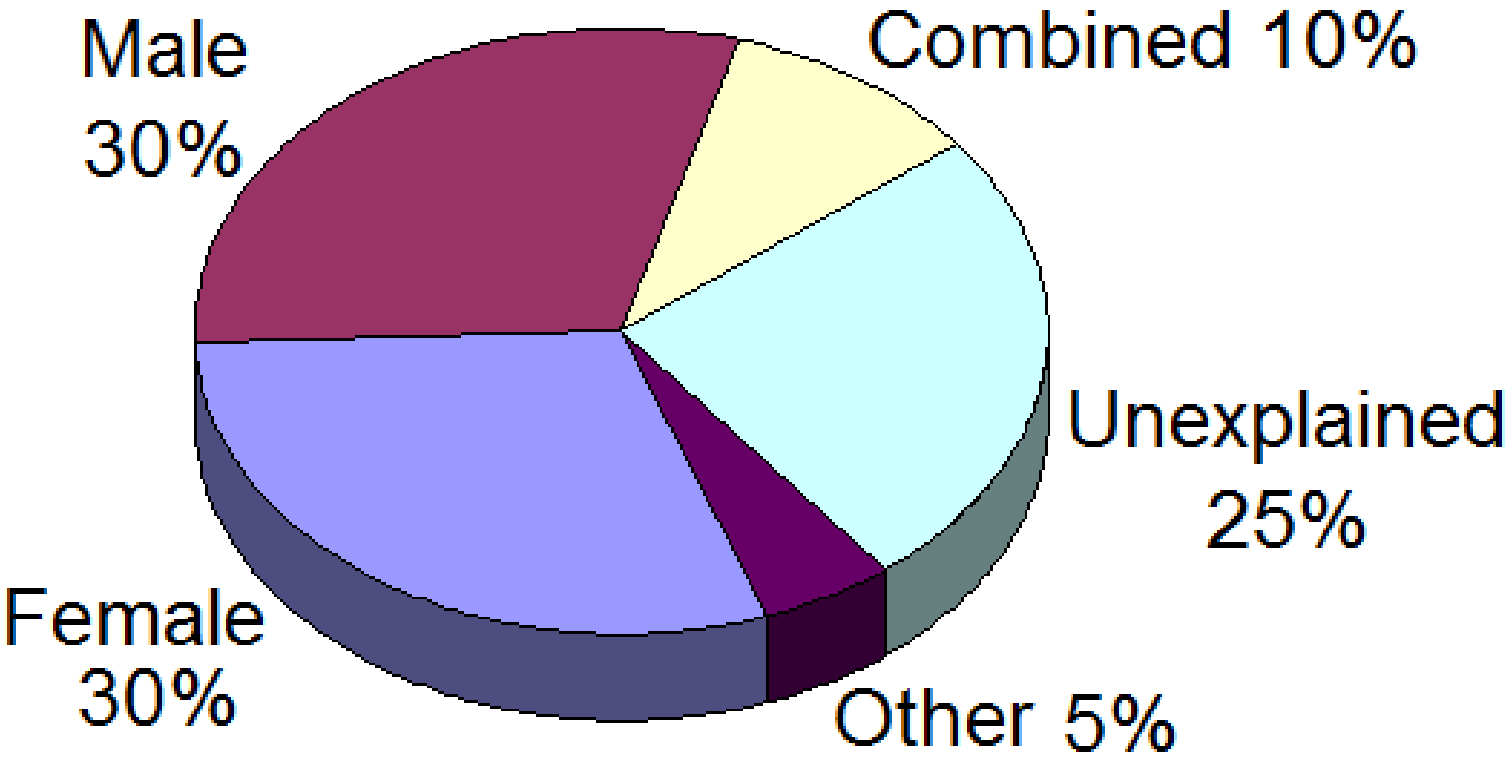
The frequency of primary infertility in married women by age groups was:

15 to 34 years	→	7.3 - 9.1 %
35 to 39 years	→	25 %
40 to 44 years	→	30 %

Chandra A, Natl Health Stat Report. 2013;57:1.

Infertility causes

Men and women equally affected



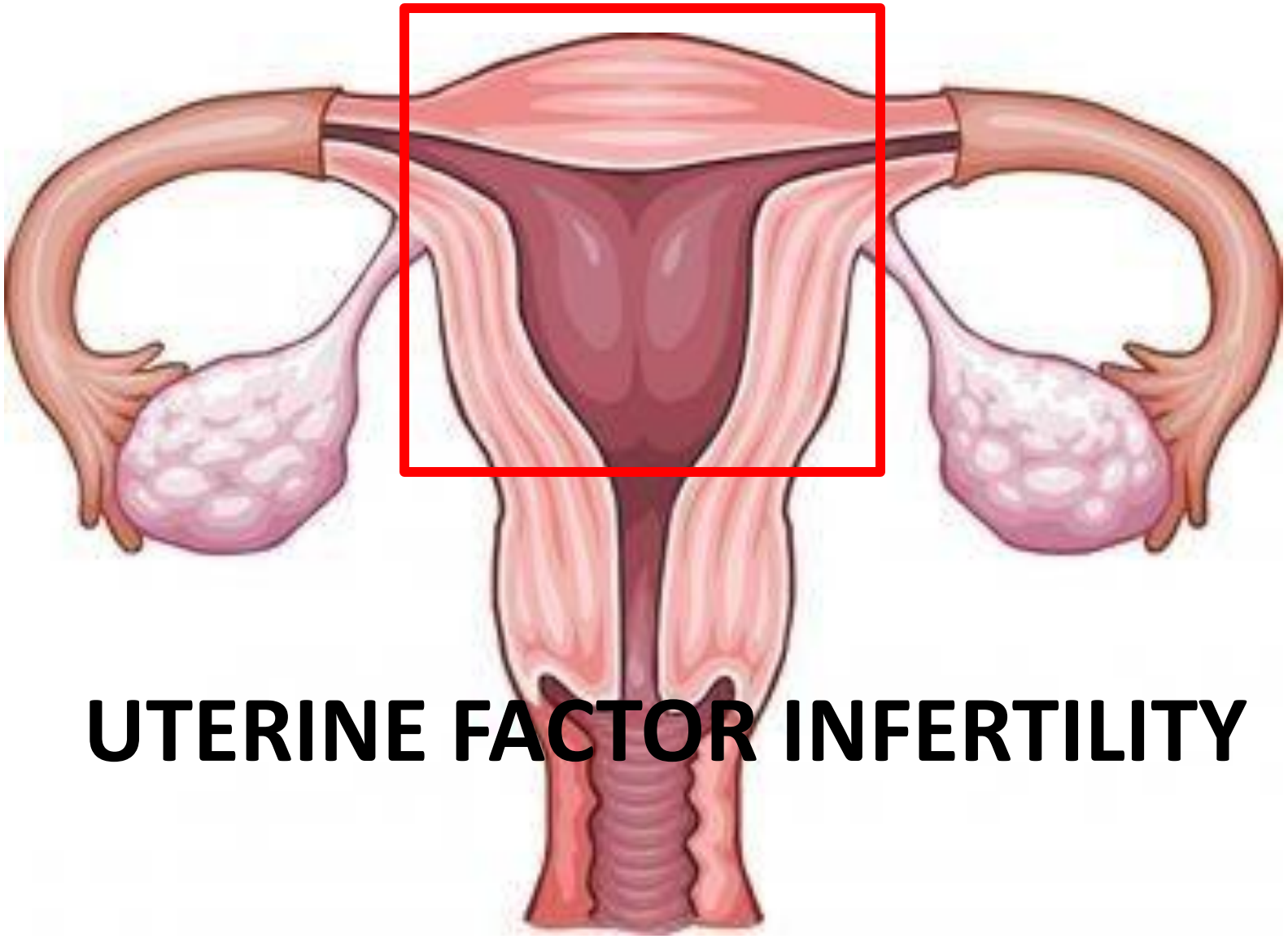
Factors affecting fertility

Female

- Age
- Over/underweight
- Stress
- Poor diet
- Athletic training
- Tobacco
- ETOH
- STD's
- Health problems

Male

- ETOH
- Drugs
- Tobacco
- Health problems
- Radiation/Chemotherapy
- Age
- Enviromental factors
  - Pesticides
  - Lead



UTERINE FACTOR INFERTILITY

INTRODUCTION

Although uterine factor comprises only a small proportion of the causes of infertility, the uterus is a fundamental component of normal reproduction and should not be overlooked during the initial infertility evaluation.

At the most basic level the uterus is essential for :

- Regeneration of the endometrium
- Sperm migration
- Embryo migration and implantation
- Nurture and protection of the fetus

Uterine factor infertility can be categorized as:

- Congenital
- Acquired

Both of them may impact a woman's ability to conceive or to sustain a pregnancy

EVALUATION OF THE UTERUS

The initial assessment of female infertility should include investigation of the female reproductive tract, evaluating for patency of the Fallopian tubes and a normal contour of the endometrial cavity.

If a uterine abnormality is suspected, more detailed evaluation of the uterine cavity may be necessary.

Since each imaging technique has inherent strenghts and limitations, a combination of several techniques allows the evaluation of a particular abnormality.

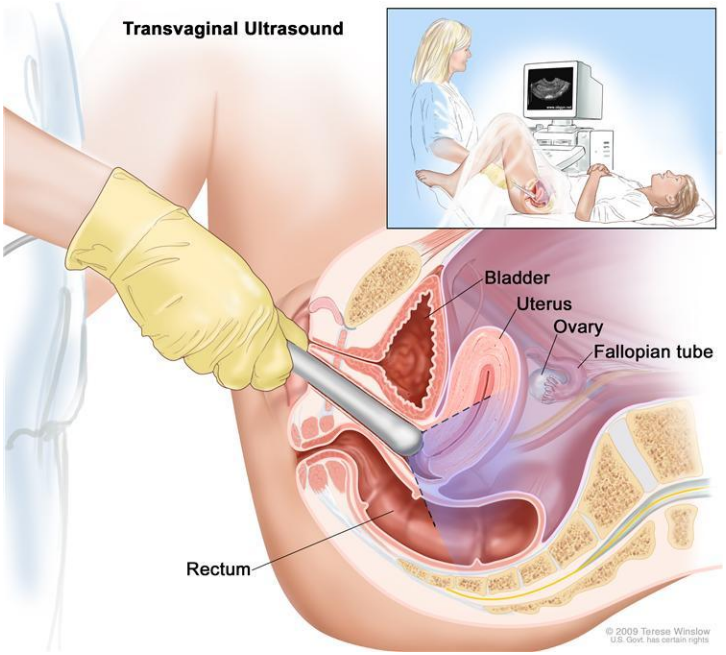
EVALUATION OF THE UTERUS

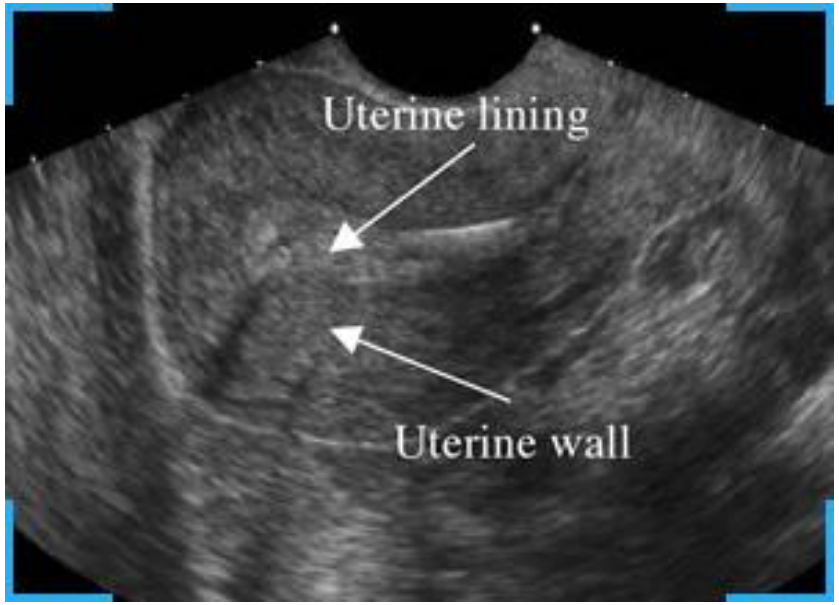
Imaging techniques include:

Transvaginal ultrasonography (TVS)

Routine diagnostic tool for assessment of the pelvis, including uterus and adnexa

Its accuracy in detecting uterine abnormalities is debated





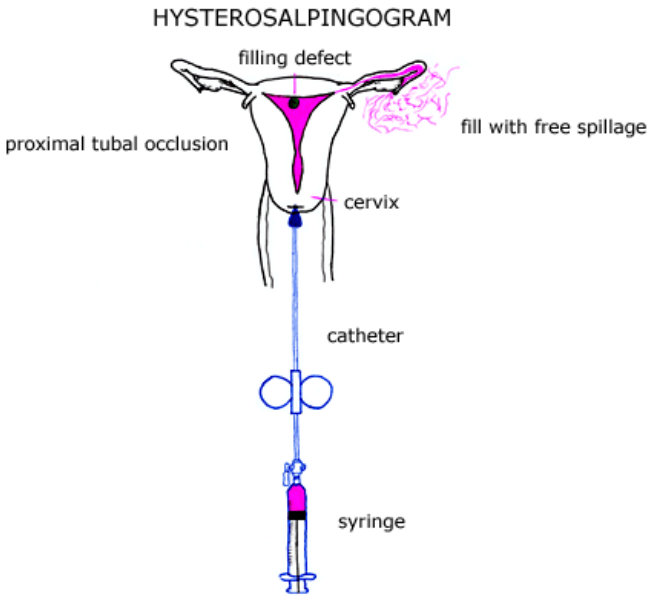
EVALUATION OF THE UTERUS

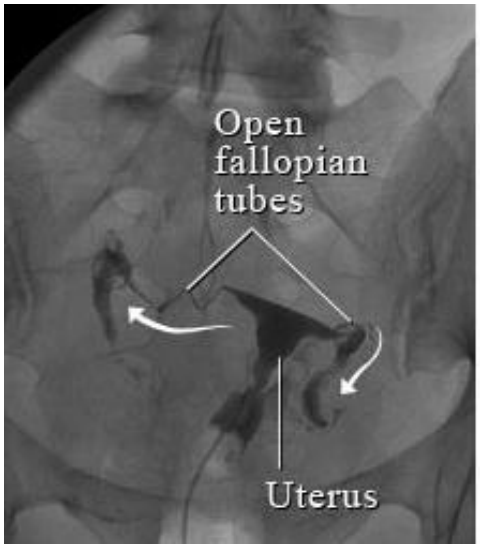
Imaging techniques include:

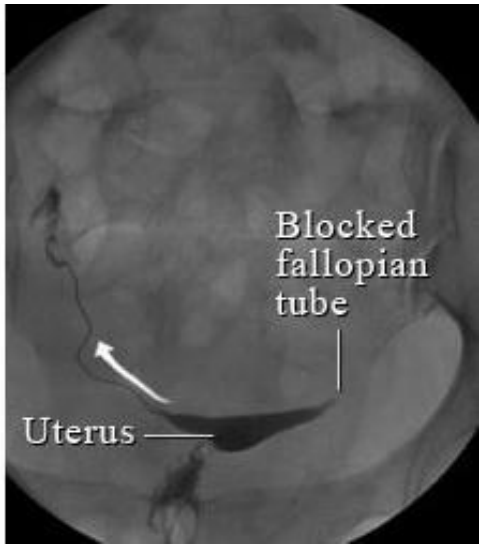
Hysterosalpingography (HSG)

Commonly used to assess the patency of the Fallopian tubes, it may provide further information about the contour of the endometrial cavity or the presence of any complex communication in the setting of uterine anomaly. X-Rays are used.

The sensitivity can be as low as 50% and the lack of information about the external uterine contour limits its utility for evaluating a uterine anomaly.







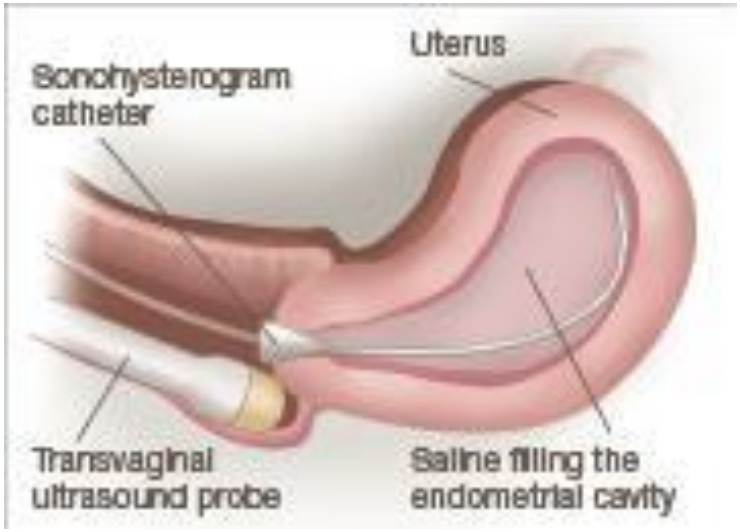
EVALUATION OF THE UTERUS

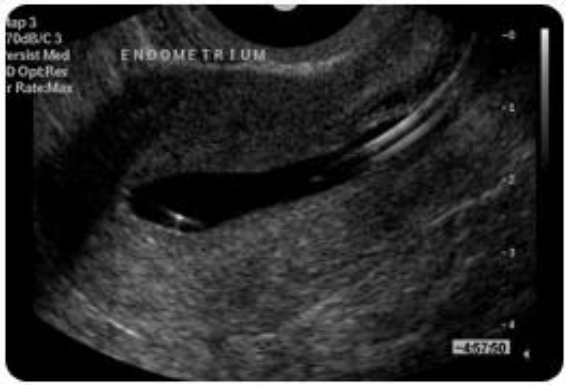
Imaging techniques include:

Saline-infusion sonography (SIS)

Superior to HSG or TVS and comparable to hysteroscopy

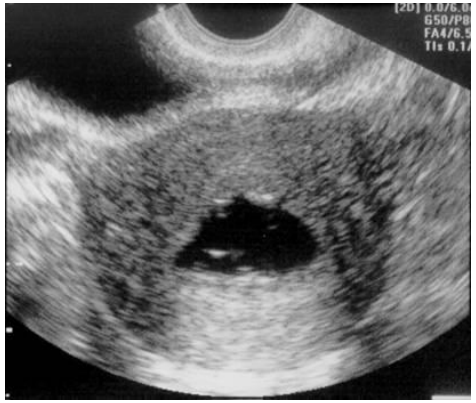
It effectively delineates the intracavitary space and internal/external uterine contours





Sagittal view

Transversal view

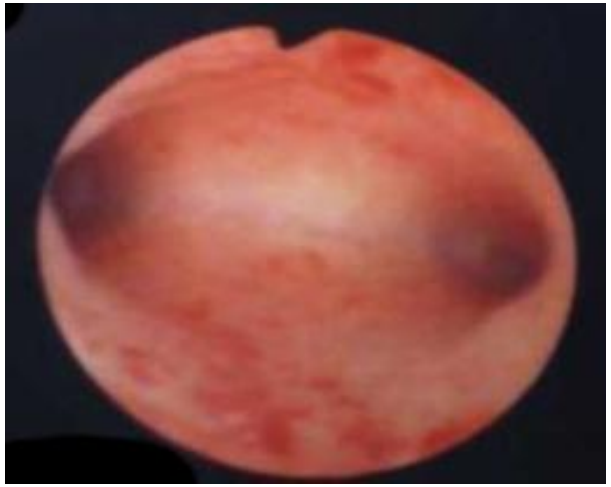


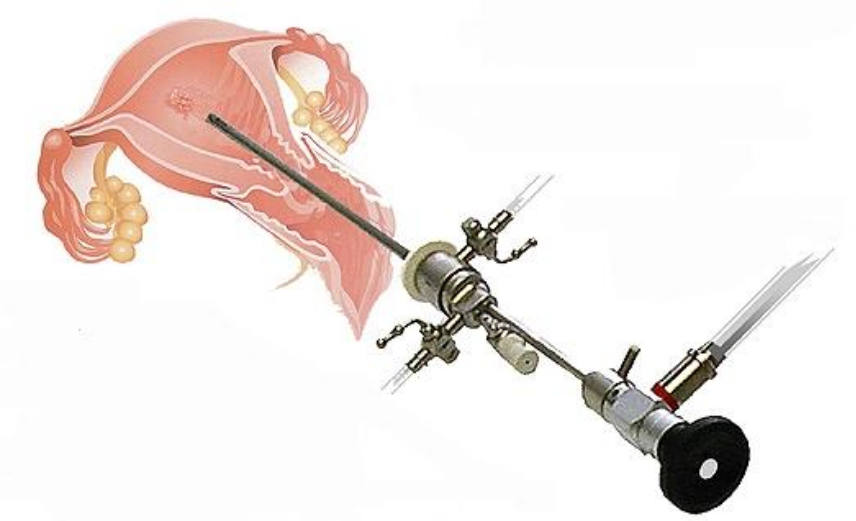
EVALUATION OF THE UTERUS

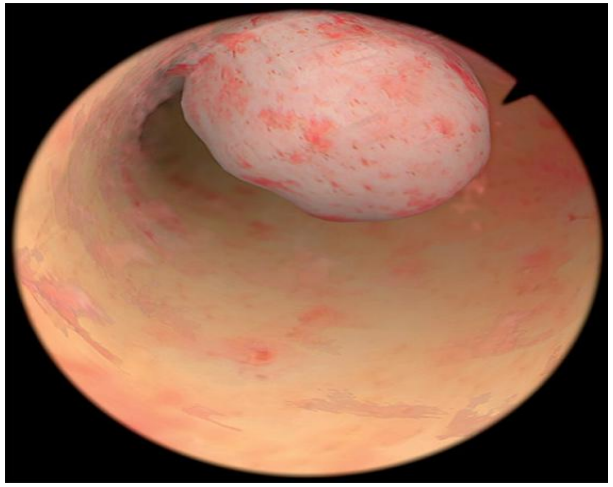
Imaging techniques include:

Hysteroscopy

Diagnosic / Operative







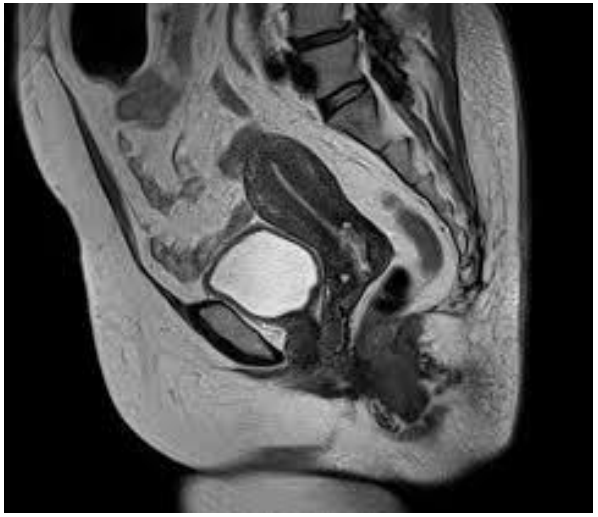
EVALUATION OF THE UTERUS

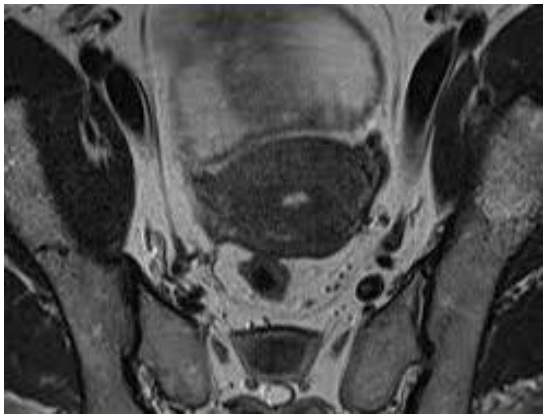
Imaging techniques include:

MRI

Excellent technique for detailed evaluation of the uterus, it is also considered the GOLD STANDARD for congenital anomalies

- ✓ Excellent delineation of internal and external uterine contours
- ✓ Determination of the extent of a uterine/vaginal septum
- ✓ Identification of rudimentary uterine structures and the presence of functional endometrium
- ✓ Differentiation between abnormalities such as leiomyomas, adenomyosis and adenomyomas





CLASSIFICATION

CONGENITAL UTERINE ANOMALIES

- General description
- Focus on Septate Uterus

AQUIRED UTERINE ANOMALIES

1. Leiomyomas
2. Endometrial polyps
3. Intrauterine adhesions
4. Adenomyosis

Congenital Uterine Anomalies

Congenital Uterine Anomalies also known as müllerian anomalies may involve the uterus, cervix, fallopian tubes or vagina.

Uterine abnormalities are the most common müllerian anomalies affecting…

- 3-4% fertile and infertile women
- 5-10% women with RPL
- 25% women with late 1^{st} /2^{nd} trimester PL or preterm delivery

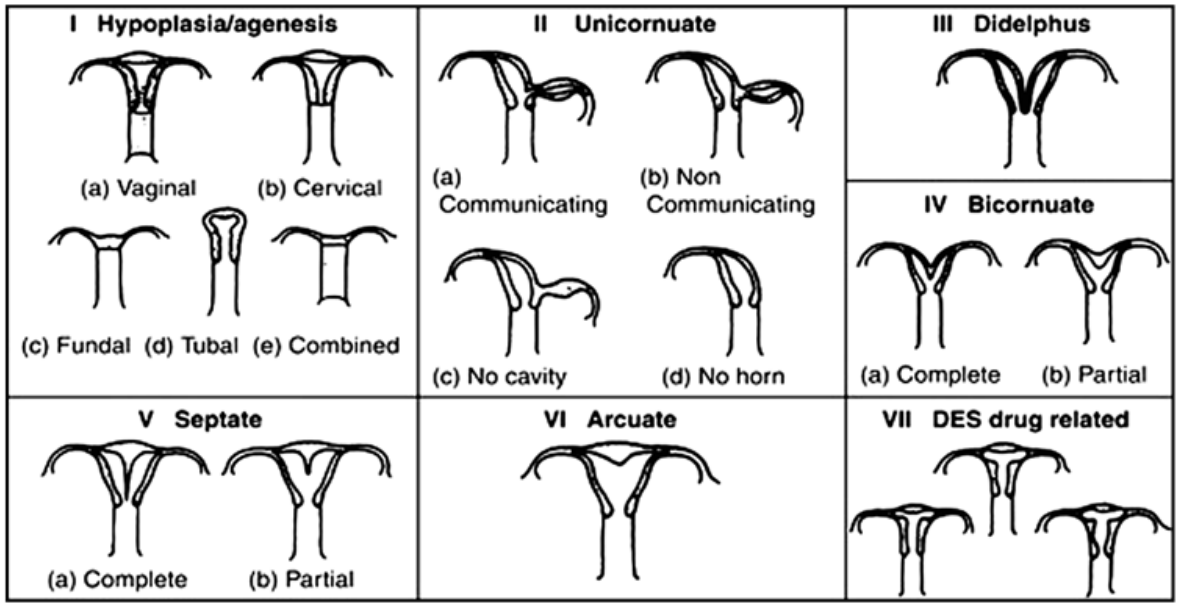
however

since they are often asymptomatic, their real prevalence remains unknown.

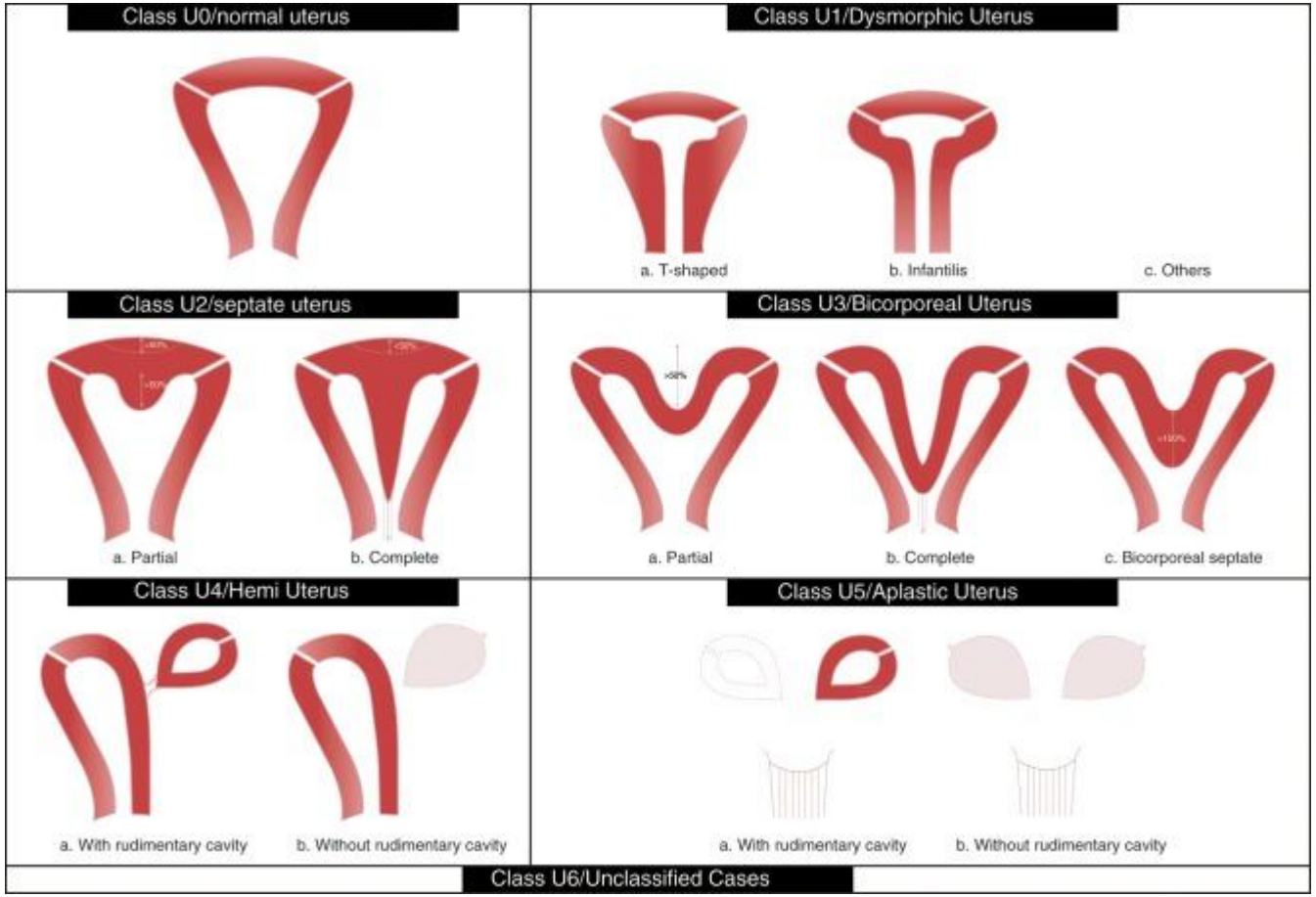
- Acceptable live birth rates
- No reported association with infertility

No need for any intervention prior conceivement, but should be closely followed during pregnancy

I	Segmental or complete agenesis or hypoplasia
II	Unicornuate uterus with or without a rudimentary horn
III	Didelphys uterus
IV	Complete or partial bicornuate uterus
V	Complete or partial septate uterus
VI	Arcuate uterus
VII	DES-related abnormalities



ESHRE/ESGE classification system for female genital tract congenital anomalies



Grimbizis, Human Reproduction 2013.

Aquired Uterine Anomalies

These anomalies include:

1. Leiomyomas
2. Endometrial polyps
3. Intrauterine adhesions
4. Adenomyosis

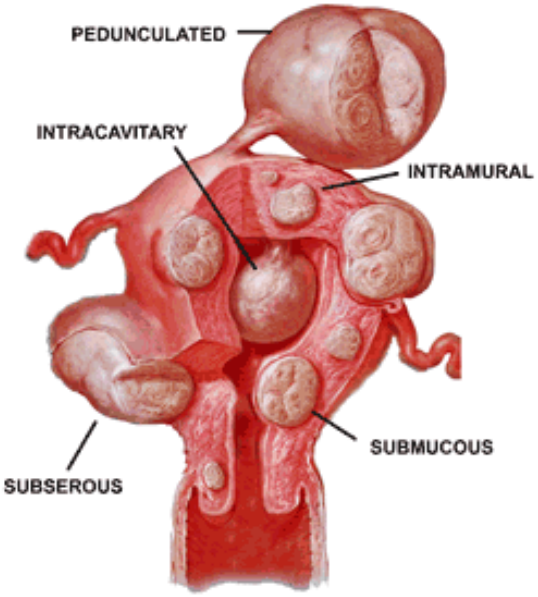
The relation between these anomalies and infertility is not well characterized

The effect of **myomas on fertility** has been best studied.

1. Uterine Leiomyomas

Most common benign tumor affecting women of reproductive age

They affect >50% 35-50 aged women and the incidence increases with age



Symptoms depend on the number, size and location of myomas.

Asymptomatic

- Pelvic pressure and discomfort
- Abnormal uterine bleeding
- Distortion of adjacent organs (bladder , bowel)

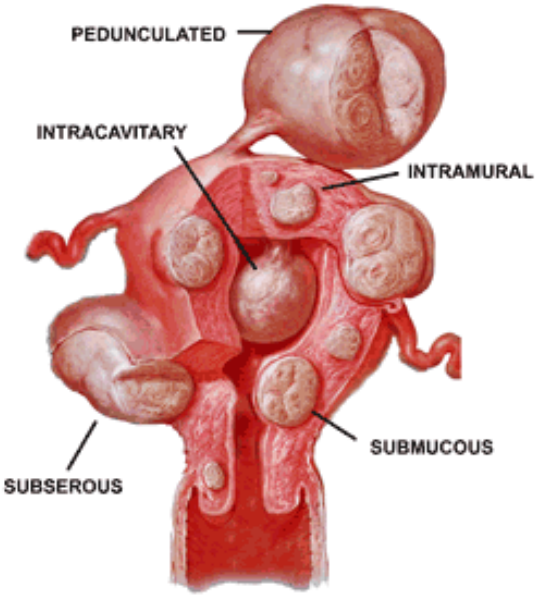
1. **Uterine Leiomyomas**-*infertility*

The position of the myomas is the most important factor responsible for a possible associated infertility

Any distortion or obstruction of the female reproductive tract may interfere with normal migration of the sperm/ovum/embryo or it may impair implantation

Possible mechanisms involved:

- Alteration of the endometrial contour
- Enlargment and deformity of the uterine cavity
- Anatomic distortion of the cervix
- Altered uterine contractility
- Persistence of intrauterine blood or clots
- Distortion or obstruction of the tubal ostia
- Implantation impairment due to the overlying endometrial damage, to the alteration of the endometrial vasculature, to endometrial inflammation, ulceration, thinning and atrophy (only for SUBMUCOSAL MYOMAS!!!)

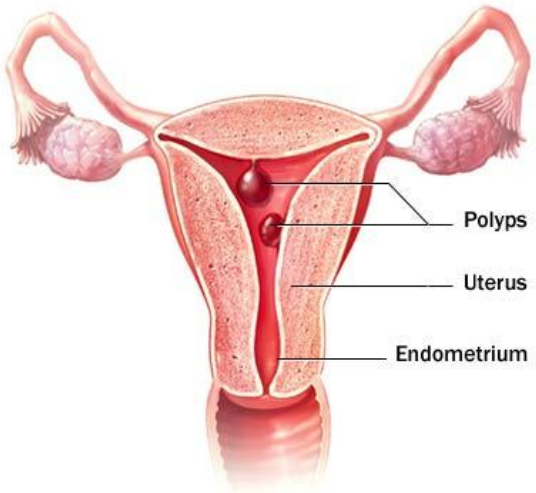


2. Endometrial Polyps

Definition

Localized hyperplastic overgrowths of the endometrium, containing both endometrial glands and stroma.

- Nature: Most of them are benign
- Number: individual/multiple lesions
- Size: can vary from mm to cm
- Shape: sessile or pedunculated



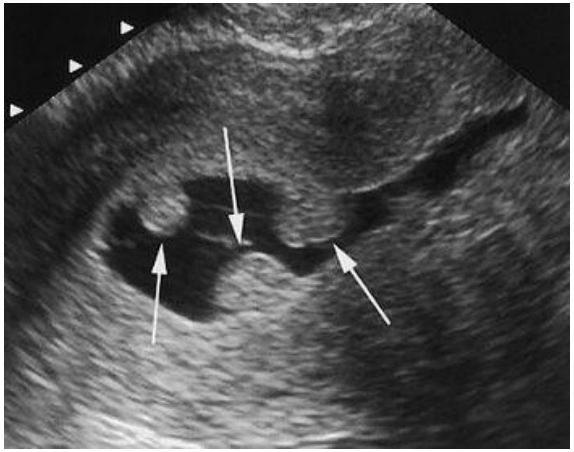
Clinical presentation

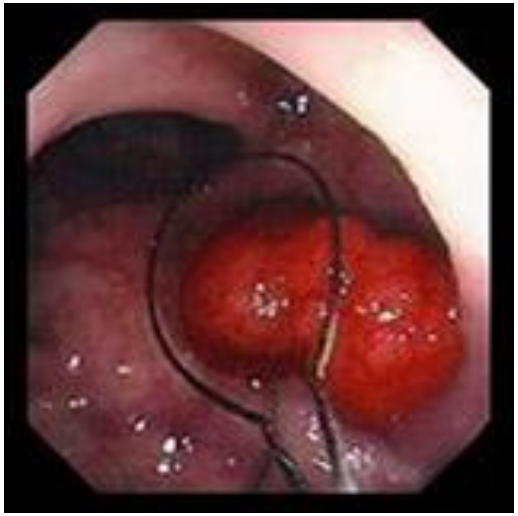
- Asymptomatic and revealed during infertility work-up (25% women with unexplained infertility)
- Symptomatic: abnormal uterine bleeding

2. Endometrial Polyps

Diagnosis

- Transvaginal sonography
- Hysterosonosalpingography→ uterine cavity-filling defect





Treatment

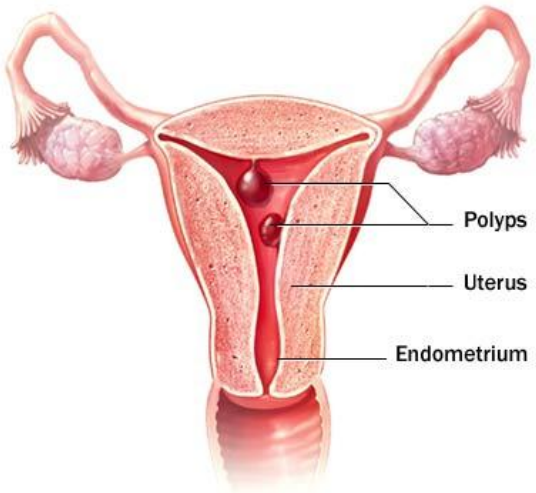
Hysteroscopy-directed polipectomy using microscissors and grasping forceps or a loop electrode prior to infertility treatment or in women at high risk of endometrial hyperplasia(chronic anovulation, obesity, personal history)

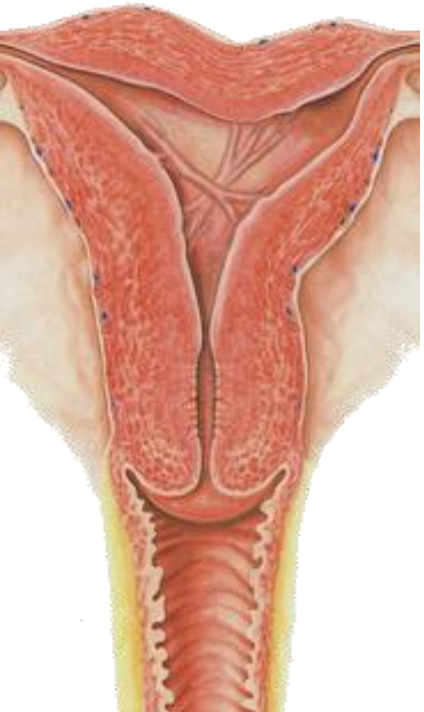
2. Endometrial Polyps

The association of endometrial polyps with **infertility** is unclear but may depend on:

- mechanical interference with sperm and embryo transport
- impairment of embryo implantation
- altered endometrial receptivity.

Moreover the size, number or location of endometrial polyps may influence any effect on the **reproductive outcomes.**





3. Intrauterine adhesions

Etiology

Intrauterine adhesions can be caused by trauma (surgical procedure or severe infection unrelated to surgery) to the basalis layer of the endometrium, with subsequent scarring between opposite areas of the myometrium.

They can result in partial or complete obliteration of the uterine cavity

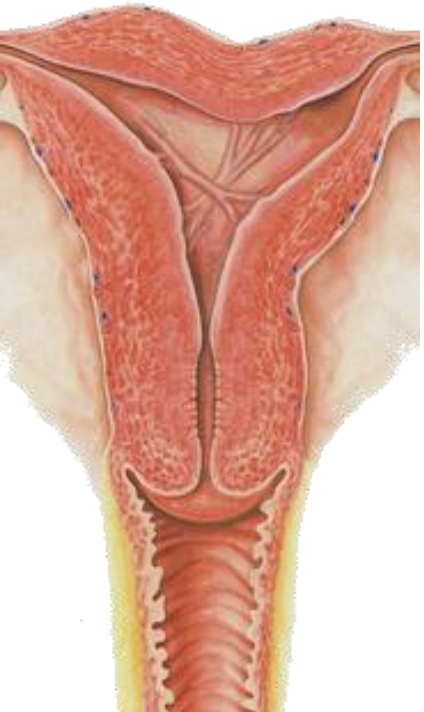
Clinical presentation

- Asymptomatic
- Symptomatic (*Asherman sdr*)→amenorrhea (the degree of menstrual disturbance does not necessarily correlate with the extent od IUA), pelvic pain, high rates of infertility, RPL

Diagnosis

- saline infusion sonogram
- Hysteroscopy→ gold standard

3. Intrauterine adhesions



Treatment

Treatment of IUA restores the anatomy of the uterine cavity and it has been shown to improve reproductive outcomes by improving fertility and reducing the rate of pregnancy loss.

Hysteroscopic adhesiolis performed with hysteroscopic scissors/ monopolar or bipolar electrosurgery/ laser ablation.

Prognosis

Postoperative adhesion reformation occurrs in 20-50% of cases, hence techniques to prevent reformation of IUA are necessary (Placement of uterine baloon catheters or intrauterine devices/ administration of estrogens±progestins/antibiotics) and postoperative evaluation of the uterine cavity is recommended, usually 1-2 months after the procedure

Postprocedure PR: 60%, Live birth rates : 40%

Success is directly related to the extent and severity of adhesions and poor endometrial development can persist due to deficiency in residual functional endometrium or to impaired endometrial perfusion

4. Adenomyosis

Definition

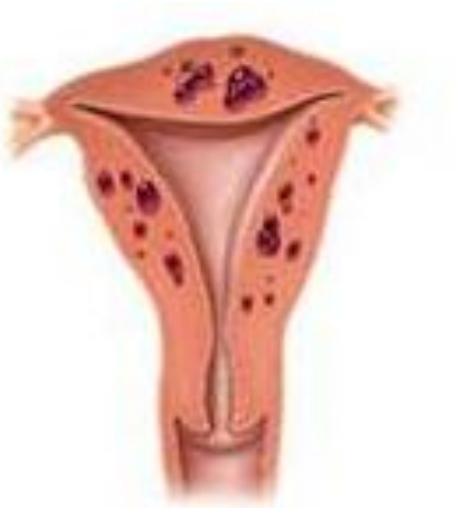
Condition in which endometrial glands and stroma have invaded the uterine myometrium

This abnormal tissue can be present in focal areas, in nodules called adenomyomas or throughout the miometrium which causes diffuse uterine enlargement

Clinical presentation

- Asymptomatic (1/3 of the women affected)
- Symptomatic (2/3 of the women affected):

  dysmenorrhea, chronic pelvic pain, menorrhagia, abnormal uterine bleeding; the frequency and severity of symptoms seems to correlate with the extent and depth of adenomyosis



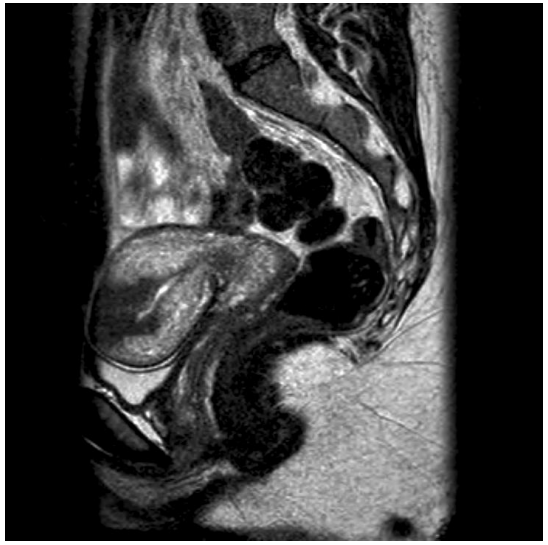
4. Adenomyosis-*diagnosis*

It is usually diagnosed in the fourth and fifth decades of life, though it can be identified in younger women and may present in the setting of infertility.

The link between adenomyosis and infertility is still unclear and further studies are needed to shed light on this issue.

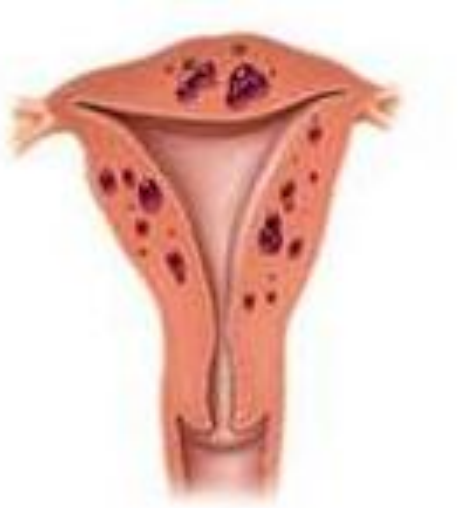
The procedures that enable the diagnosis are:

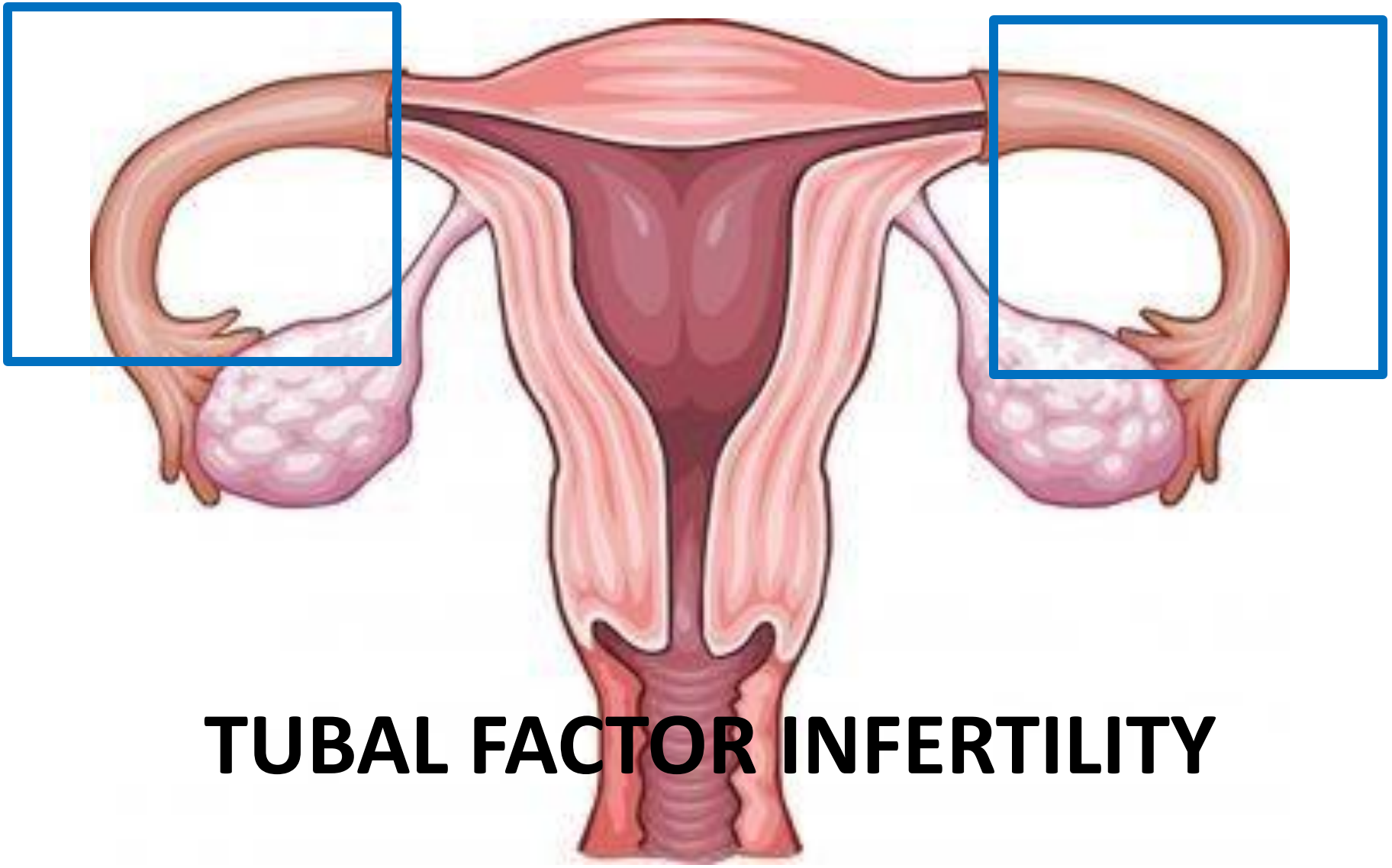
- Transvaginal sonography→ heterogeneous myometrial echotexture
- MR→increased signal intensity within the miometrium and/or a thickened junctional zone
- Histologic evaluation of a histerectomy specimen → allows definitive diagnosis



4. Adenomyosis-*treatment*

MEDICAL	OCPs, levonorgestrel releasing intrauterine device, GnRH-a, aromatase inhibitors	Improvement in adenomyosis-related symptoms	Precludes pregnancy	Conservative treatment options such as hormone therapy, vessel embolization and combined surgical and hormonal treatments should be further studied
SURGICAL	endoscopic endometrial ablation or hysterectomy		not appropriate for women with desired fertility	





TUBAL FACTOR INFERTILITY

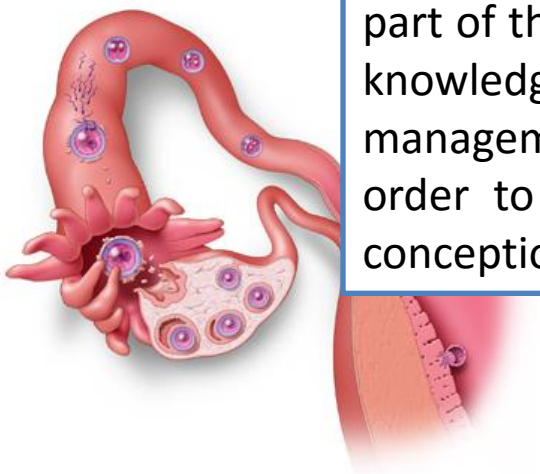
INTRODUCTION

30% infertile couples have complete or partial blockage of a fallopian tube.

- Transient/permanent
- Distal/proximal
- Unilateral/Bilateral

thus

Evaluation of the tubal patency should be part of the standard infertility work-up and knowledge of the various diagnostic and management strategies is essential in order to maximize a patient's chance of conception



ETIOLOGY

Pelvic inflammatory disease (PID) (in >50% cases)	**Chlamydia trachomatis, Neisseria gonorrhea, and anaerobic organisms are the most common organisms that infect the lower genital tract and cause PID. In women diagnosed with PID, the risk of infertility increased with the number and severity of pelvic infections**
Endometriosis	Chronic inflammation from the reactive cytokines and chemokines produced by the ectopic endometrium results in scarring similar to that observed in PID. The long-term consequence of the inflammation is often distal tubal adhesive disease and occlusion.
Pelvic tubercolosis	Only in the developing countries!!!
Pelvic and abdominal surgery	Scarring and adhesions
Myomas near the tubal ostium	occlude the cornua and interstitial portion of the fallopian tube, causing or creating the appearance of proximal fallopian tube blockage.
Bilateral tubal ligation	
Pelvic pathologies	Ruptured appendix, ectopic pregnancy

INTRODUCTION

ETIOLOGY

CLASSIFICATION

DIAGNOSIS

1. Laparoscopic chromoperturbation
2. Hysterosalpingography (HSG)
3. Sonohysterography (SHG)
4. Hysterosalpingo-contrast sonography (HyCoSy)
5. Salpingoscopy
6. Chlamydia serology

MANAGEMENT

- PROXIMAL TUBAL DISEASE
  - Tubocornual anastomosis
  - Selective salpingography and transcervical tubal cannulation
- DISTAL TUBAL DISEASE
  - Salpingostomy
- HYDROSALPINGES
- ADHESIONS
- STERILIZATION REVERSAL

ETIOLOGY

Pelvic inflammatory disease (PID) (in >50% cases)

endometriosis

Pelvic tubercolosis

Pelvic and abdominal surgery

Myomas near the tubal ostium

Bilateral tubal ligation

Pelvic pathologies

→ tubal obstruction

endosalpingeal destruction

periadnexal adhesions

→ TUBAL OCCLUSION

INTRODUCTION

ETIOLOGY

CLASSIFICATION

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MANAGEMENT

- PROXIMAL TUBAL DISEASE
  - Tubocornual anastomosis
  - Selective salpingography and transcervical tubal cannulation
- DISTAL TUBAL DISEASE
  - Salpingostomy
- HYDROSALPINGES
- ADHESIONS
- STERILIZATION REVERSAL

CLASSIFICATION

	Distal tubal disease	Proximal tubal disease
Frequency	More common (85%)	Less common (15%)
Etiology	•Obstruction often due to peritubal pelvic adhesions •Prior tubal sterilization •Salpingitis •Endometriosis	•Infection •Endometriosis •Tubal polyps •Congenital occlusion
Classification	Mild/Moderate/Severe based on size of hydrosalpinx, presence of fymbria and degree of adhesions	
PR	Mild→80% Moderate →31% Severe disease→16%	

DIAGNOSIS

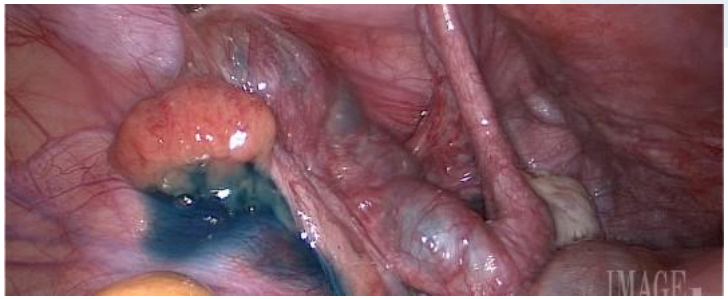
1. **Laparoscopic chromoperturbation**
2. **Hysterosalpingography (HSG)**
3. **Sonohysterography (SHG)**
4. **Hysterosalpingo-contrast sonography (HyCoSy)**
5. **Salpingoscopy**
6. **Chlamydia serology**

DIAGNOSIS

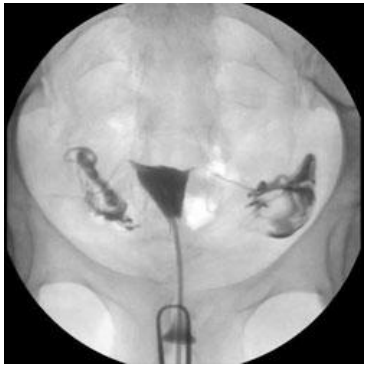
1. Laparoscopic chromoperturbation

Injection of diluted indigo carmine into the uterine cavity with simulataneous laparoscopic visualization to evaluate for tubal fill and spill into the abdominal cavity

PROs	CONs
Gold standard for the evaluation of fallopian tubes	invasive
	Expensive
	Need for anestesia
	Small but real mortality risk



HSG and HyCosy are safer and more economical alternatives!!!!



DIAGNOSIS

2. Hysterosalpingography (HSG)

Injection of a radio-opaque contrast material (either oil or water-based) into the uterine cavity under fluoroscopic visualization

PROs	CONs
Excellent at visualizing obstruction (specificity 83%)	tubal spasm that may lead to a false diagnosis of proximal tubal blockage
Speed	inability to detect peritubal adhesions
Lack of need for anesthesia	iodinated contrast dye has a small risk of allergic-like reaction
Possible therapeutic role of the contrast media, both by flushing tubal debris and preventing mast cell phagocytosis of spermatozoa.	risk of infection

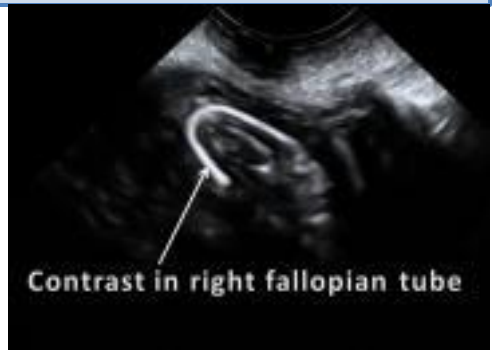
DIAGNOSIS

3. Sonohysterography (SHG)

A saline solution is injected transcervically and transvaginal ultrasound is mainly used to assess for uterine anomalies.

PROs	CONs
Low cost and well-tolerated alternative method to HSG	Small risk of infection*
	The presence of postprocedure free fluid in the pouch of Douglas can suggest tubal patency, but it is not confirmatory and is limited by the fact that one cannot determine if the saline spilled from one or both tubes
	it does not allow the distinction between proximal and distal obstruction

HyCoSy is used as an alternative method to increase the accuracy of SHG



DIAGNOSIS

4. Hysterosalpingo-contrast sonography (HyCoSy)

In this procedure air contrast is added to assess the passage of bubbles through the tubes

This method is superior to HSG and comparable with chromoperturbation.

BENEFITs compared to HSG	CONs
patient tolerance	Small risk of infection*
avoidance of iodinated contrast medium and ionizing radiation	
less expensive	

Increased in patients affected by PID or hydrosalpinx, who are prescribed prophylactic antibiotics

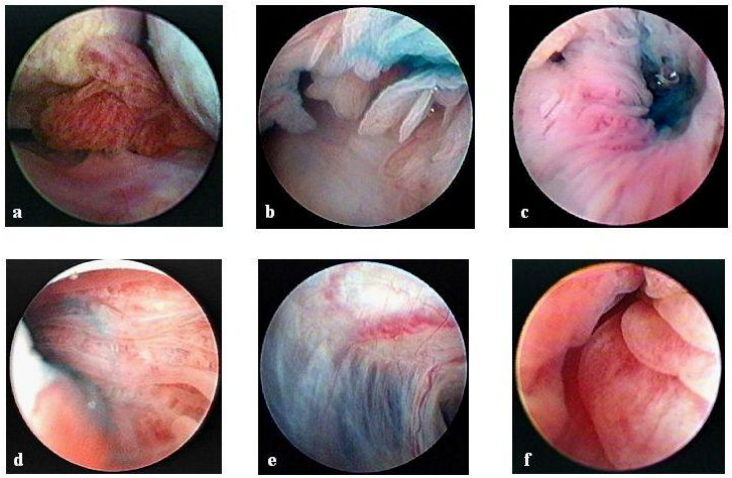
DIAGNOSIS

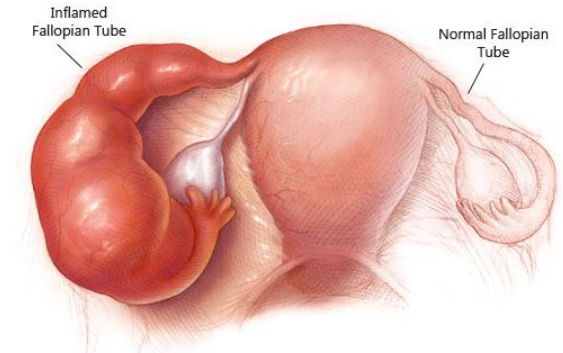
5. Salpingoscopy

Endoscopic evaluation of tubal mucosa, including visualization of mucosa flattening and intraluminal adhesions.

It allows the assessment of internal **BUT NOT EXTERNAL** anatomy

It is rarely used as a part of the basic infertility work-up, as it is **invasive** and often complicated by **tubal perforation**





DIAGNOSIS

6. Chlamydia serology

Chlamydia trachomatis is the main cause of PID.

Since the antibody response to chlamydia heat shock protein 60 predicts subsequent risk of tubal infertility, evaluation for chlamydia antibody titers has been proposed as a low-cost, non-invasive method of assessing tubal status.

however

Even though it is not invasive

It does not provide anatomical and prognostic information

And it cannot serve an interventional role

Thus, it is used only in patients:

Allergic to dye

With limited finances

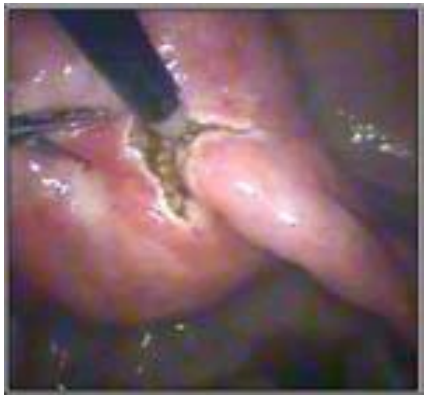
MANAGEMENT

- **PROXIMAL TUBAL DISEASE**
  - Tubocornual anastomosis
  - Selective salpingography and transcervical tubal cannulation
- **DISTAL TUBAL DISEASE**
  - Salpingostomy
- **HYDROSALPINGES**
- **ADHESIONS**
- **STERILIZATION REVERSAL**

MANAGEMENT

- **PROXIMAL TUBAL DISEASE**
  - Tubocornual anastomosis

    Excision of the diseased proximal tube, followed by axial incision of patent residual tube along its antimesenteric border and reimplantation.
    PR after Microsurgical technique: 50%
    PR after Macrosurgical technique: 25%



  - Selective salpingography and transcervical tubal cannulation

    Fluoroscopic/hysteroscopic placement of a cannula at the tubal ostium, followed by injection of contrast dye under fluoroscopic or laparoscopic visualization. Increased hydrostatic pressure from the dye may clear the debris, otherwise a atraumatic guide wire is threaded through the oviduct.

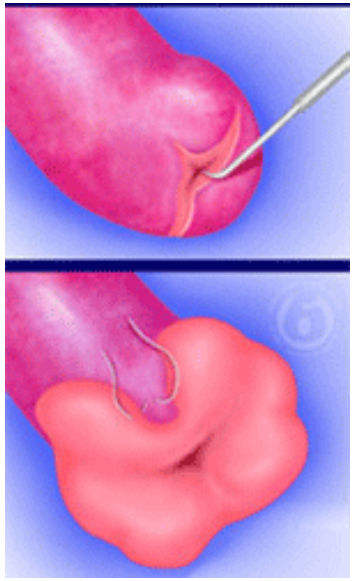
MANAGEMENT

- **DISTAL TUBAL DISEASE**
  - Salpingostomy

    It consists in creating a new stoma at the occluded part of the distal tube→overall PR = 30% .

    Higher PR are obtained with microsurgical procedures and in case of mild disease

    Indication: young women with mild distal tubal disease



MANAGEMENT

- **HYDROSALPINGES**

A **hydrosalpinx** is a distally blocked Fallopian tube filled with serous or clear fluid. The blocked tube may become substantially distended giving the tube a characteristic sausage-like or retort-like shape.

Hydrosalpinx decreases live birth rates after ART by about one-half.

Several mechanisms have been proposed to explain the link between hydrosalpinx and infertility:

•Embryotoxic effect of the fluid

•Decreased implantation due to leakage of the fluid into the endometrial cavity

•Flushing of the embryo by fluid

TREATMENT→SALPINGECTOMY

The term salpingectomy refers to the surgical removal of the Fallopian tube, that is severed at the point where it enters the uterus. This procedure can be performed via laparotomy or via laparoscopy (more recently)

Recent evidence has shown that unilateral salpingectomy for unilateral hydrosalpinx and bilateral salpingectomy for bilateral salpinx should be recommended. Moreover the odds of pregnancy and live birth rates increased in patients with ultrasound-visible hydrosalpinx who underwent salpingectomy prior to ART. Thus, this procedure should be performed immediately in case of ultrasound-visible hydrosalpinx in order to optimize the results of ART.

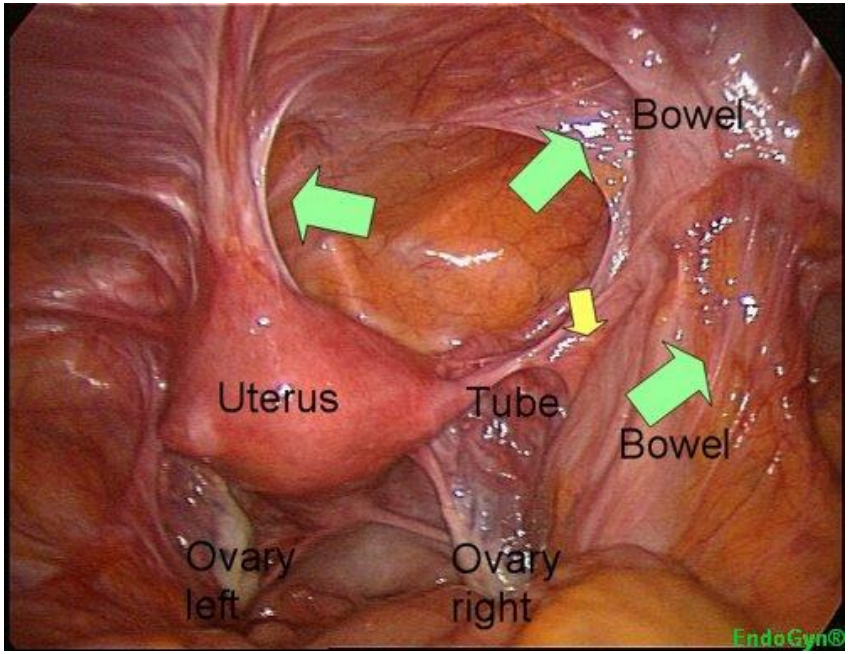
An alternative procedure involves the DRAINAGE OF THE HYDROSALPINX FLUID, but data about the results of this approach are still lacking.

MANAGEMENT

- **ADHESIONS**

  Adhesions should be treated via laparoscopic lysis, since it results in fewer and less dense postoperative adhesions and it increases the chance of intrauterine pregnancies compared to ectopic pregnancies.

  Adhesion may be ablated using the cold knife, elecrocautery or laser.

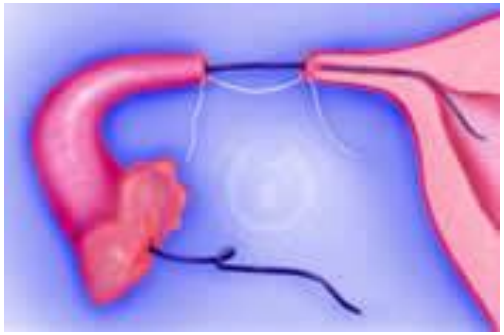


MANAGEMENT

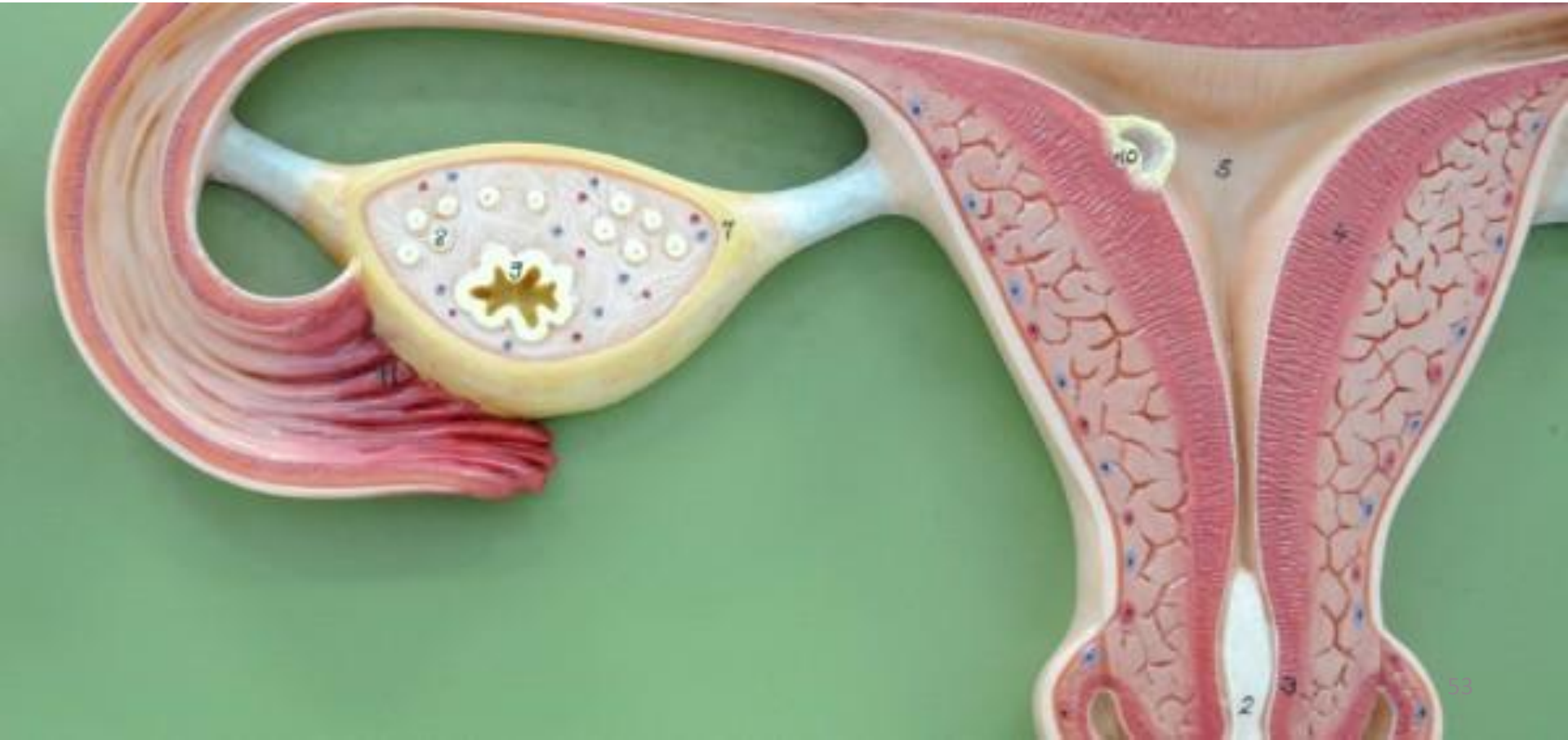
- **STERILIZATION REVERSAL**

  Tubotubal reanastomosis is traditionally achieved by laparotomy after laparoscopic assessment of the fallopian tubes. If one or both fallopian tubes are judged to be repairable, then the occluded ends of the proximal and distal segments are opened and the ends are anastomosed with a fine nonreactive suture.

  The prognosis for fertility after tubal sterilization depends on multiple factors, such as the method of sterilization (after ring/clip placement>>electrocautery), lenght of adequate residual tube, age of the patient and presence of other tubal pathology.



TECNICHE DI PMA



Assisted Reproductive Techniques (ART)

Any treatment that deals with “means of conception other than vaginal intercourse” is termed as ART.

NICE guideline 2013

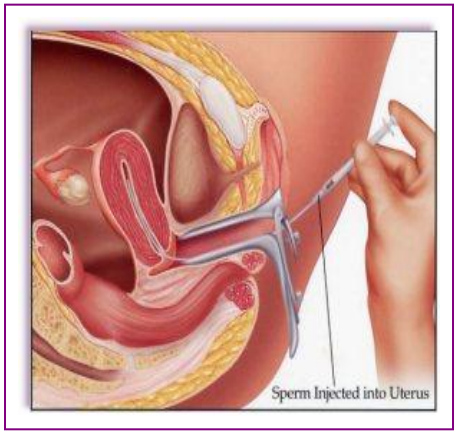
Gradual approach from less invasive to more invasive techniques

- **IUI** – Intra Uterine Insemination (Husband/Donor)
- **IVF + ET** – In Vitro Fertilization + Embryo transfer
- **ICSI** – Intra Cytoplasmic Sperm Injection

INTRA UTERINE INSEMINATION
IUI

IUI

Injection of washed prepared sperms into the uterine cavity through a fine catheter during peri-ovulatory phase in a natural or stimulated cycle.



IUI

The procedure may help in increasing the chances of pregnancy in following ways

1. Allowing sperm-ovum contact close to the **date and time of ovulation (synchronization)**
2. By bringing the sperm **very close to the site of fertilization** and by passing the cervical factors
3. Sperm preparation increases the **sperm density and removes all antigens on the surface of sperm and in seminal plasma**

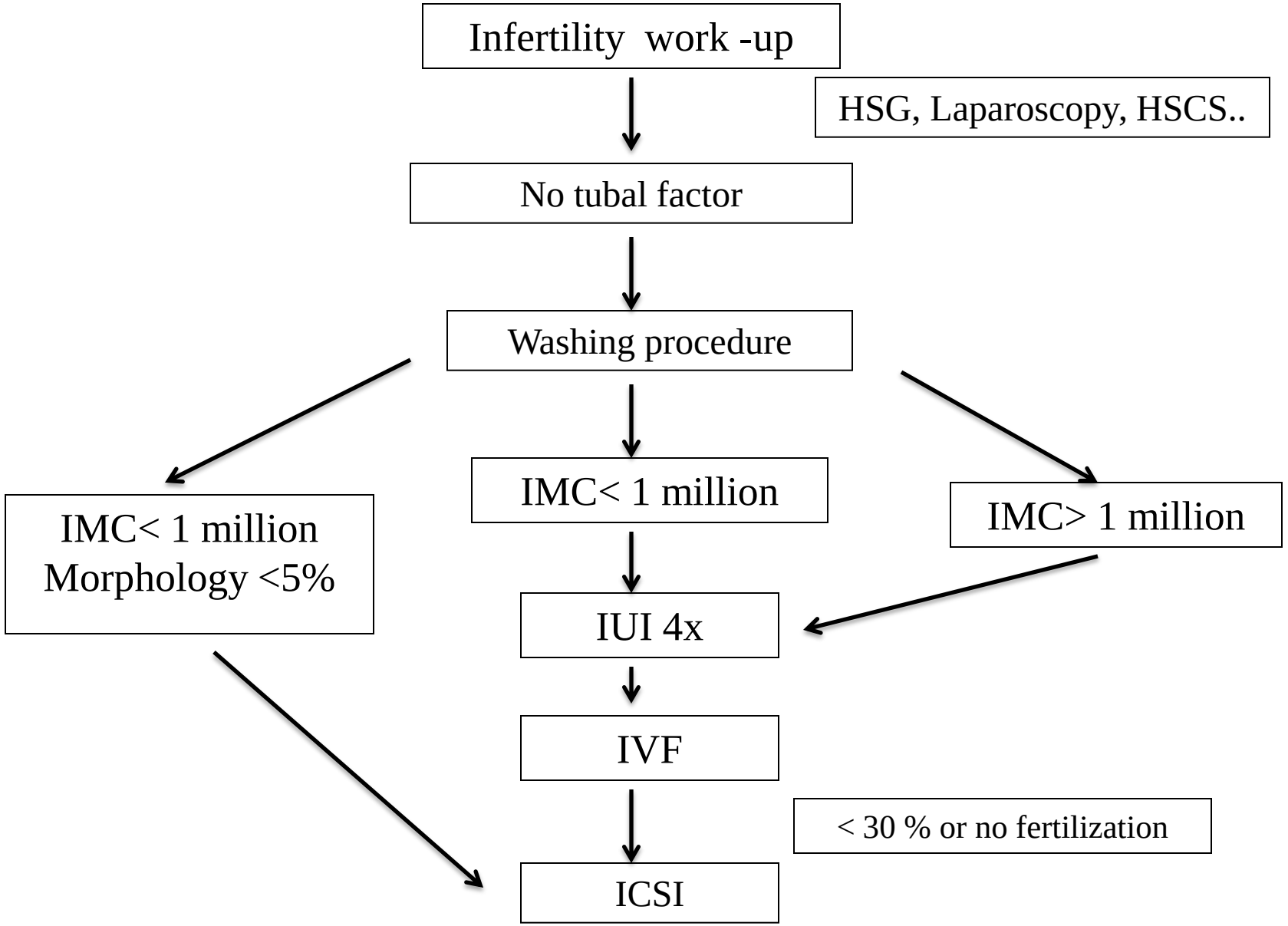
Indications for Intra Uterine Insemination (IUI)

At least one Fallopian tube must be normal and patent !!!

- Mild male infertility
- Unexplained infertility
- Ovulatory dysfunction, PCOS
- Mild endometriosis
- Cervical factors
- Coital problems
- Immunological factors
- HIV, HBs Ag, HCV infection
- Donor Sperm

IUI and COS increase the live birth rate

IUI increases the live birth rate when compared to TI

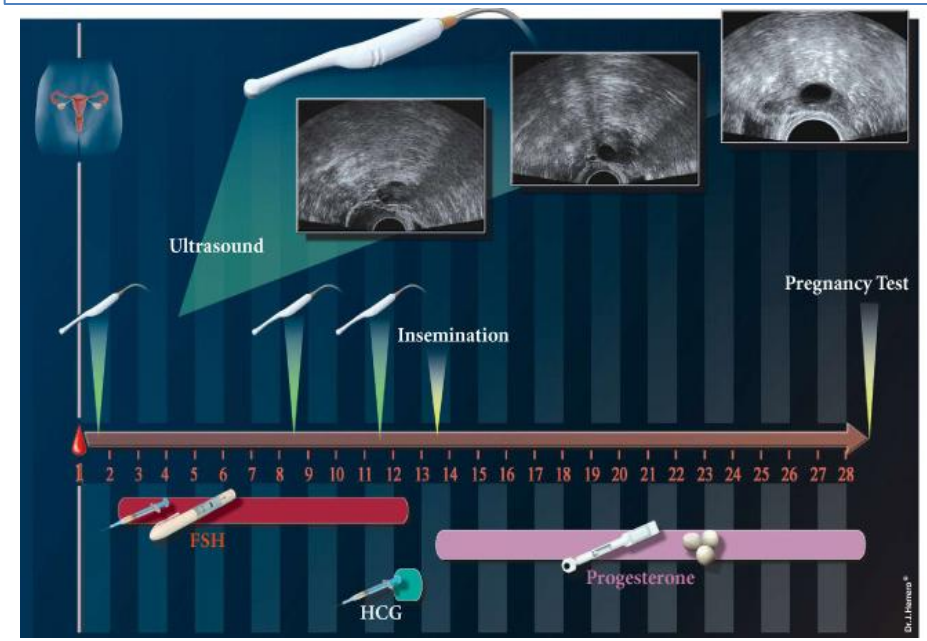


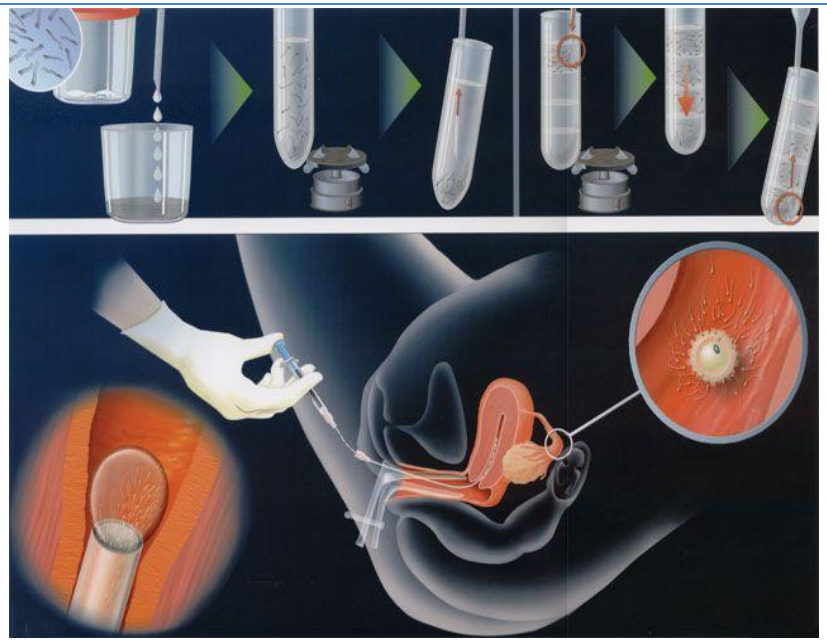
Proposed algorithm of male subfertility treatment at the Genk Institute for fertility Technology (ICM, insemination motile count of the number of motile spermatozoa after washing procedure; HSG, hysterisalpingography; HSCS, hysatero-salpingo-contrast-sonography)

Ombelet W et al 2008). ESHRE Monograph , 1: 64-72

IUI : Step by Step

1. Patient's selection
2. Natural cycle or
3. Controlled Ovarian stimulation.
4. Monitoring of treatment, to measure the growth of follicles, individualize drug doses, and prevent hyper stimulation.
5. Sperm preparation
6. Insemination
7. Luteal support.





Selection of patients

- A valid indication for IUI
- Normal or mildly abnormal semen parameters *(Semen analysis within 3 months of the planned IUI)*
- No evidence of intrauterine disease and patent tubes (at least one) as shown in *a Recent HSG or (laparoscopy / hysteroscopy)*
- Female age < 43 years ? (Day 3 FSH < 10-15 mIU/Ml, if age > 37 yrs)

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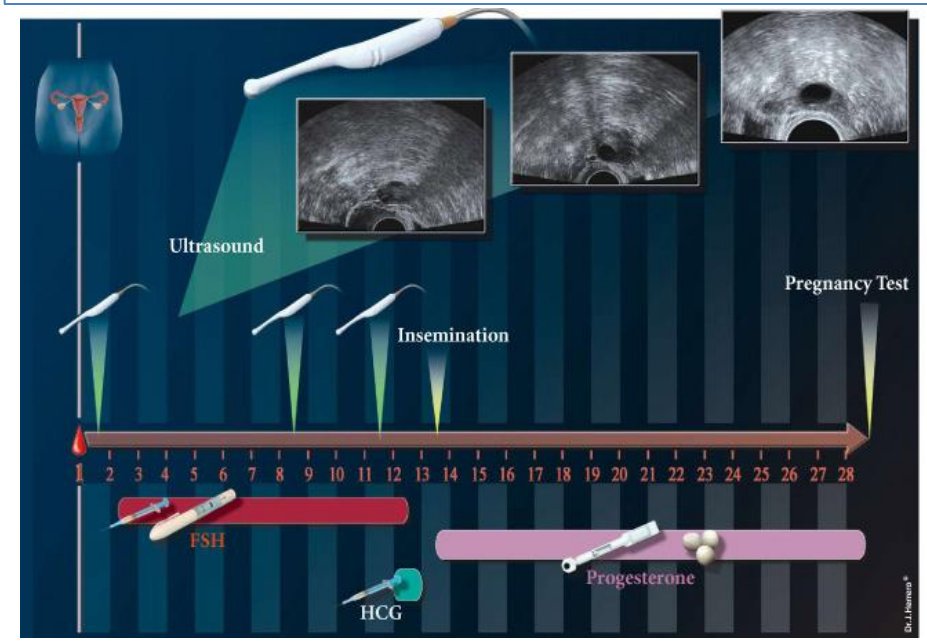

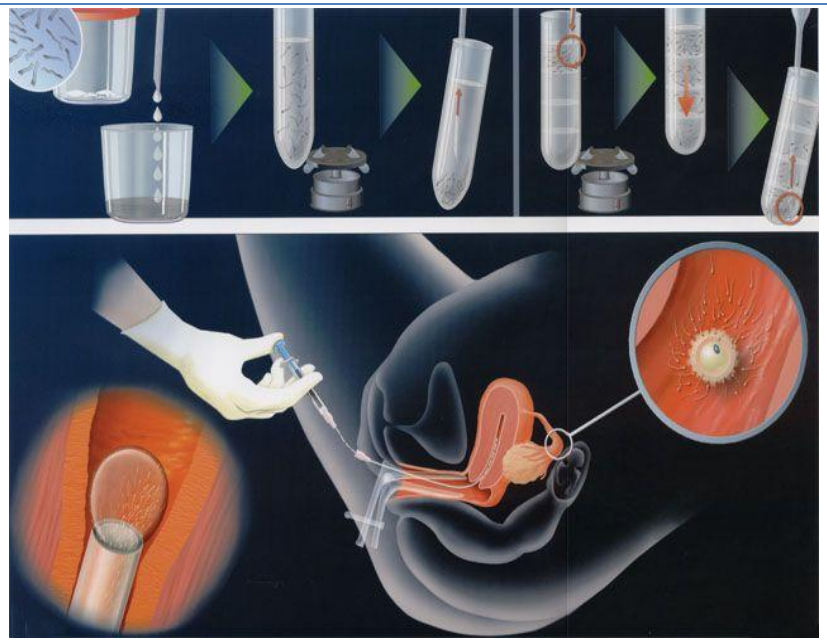

2.Protocol of natural cycle IUI

- Monitoring begins 16 days before expected menses by TVS for follicular maturation.
- Once a mature sized follicle of 18-24 mm & > 9mm trilaminar endometrium are obtained the woman will monitor urinary LH every 4-5 hours.
- Intrauterine insemination is timed 36-40 hours from the LH surge and will be repeated within 12 hours if the oocyte had not released as yet.

IUI : Step by Step

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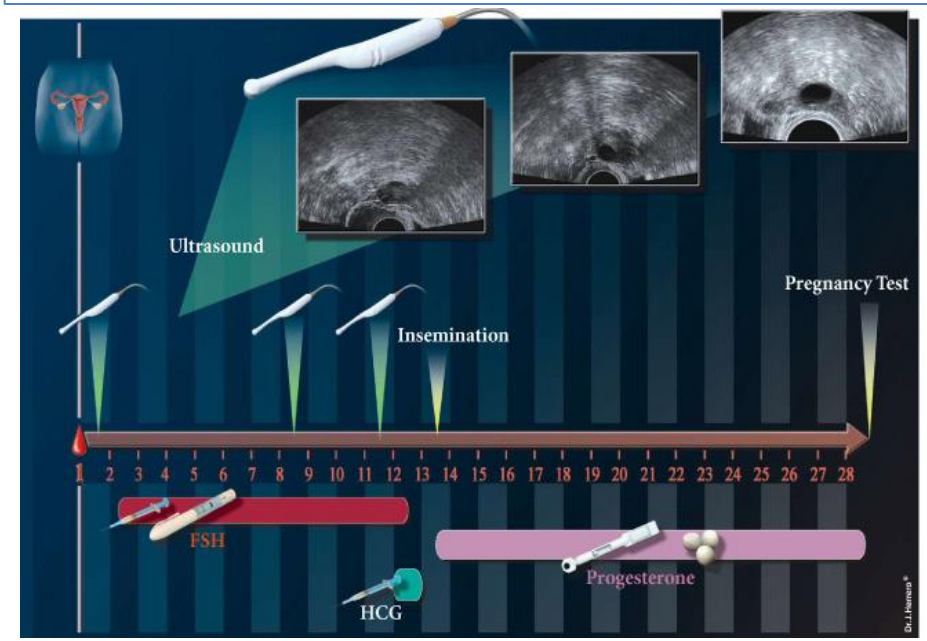
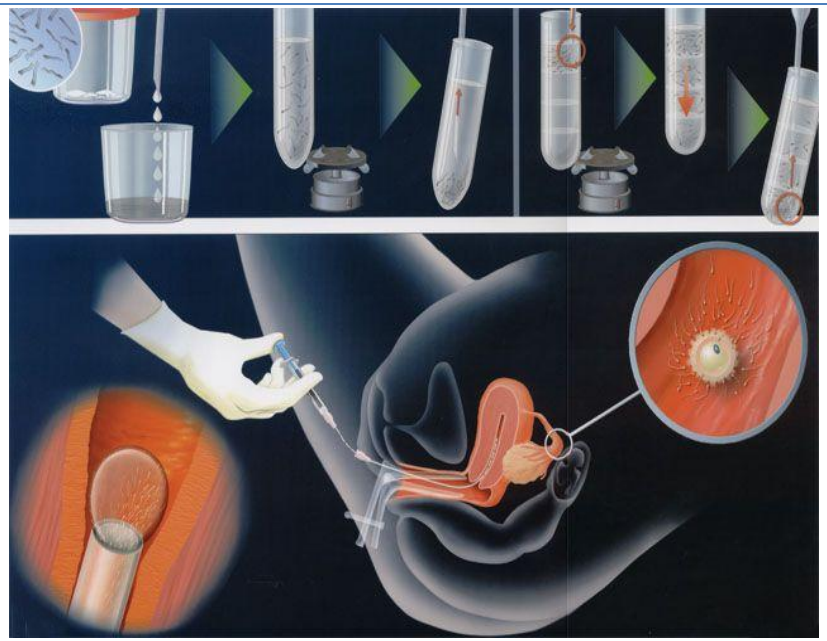




Controlled ovarian hyperstimulation before IUI

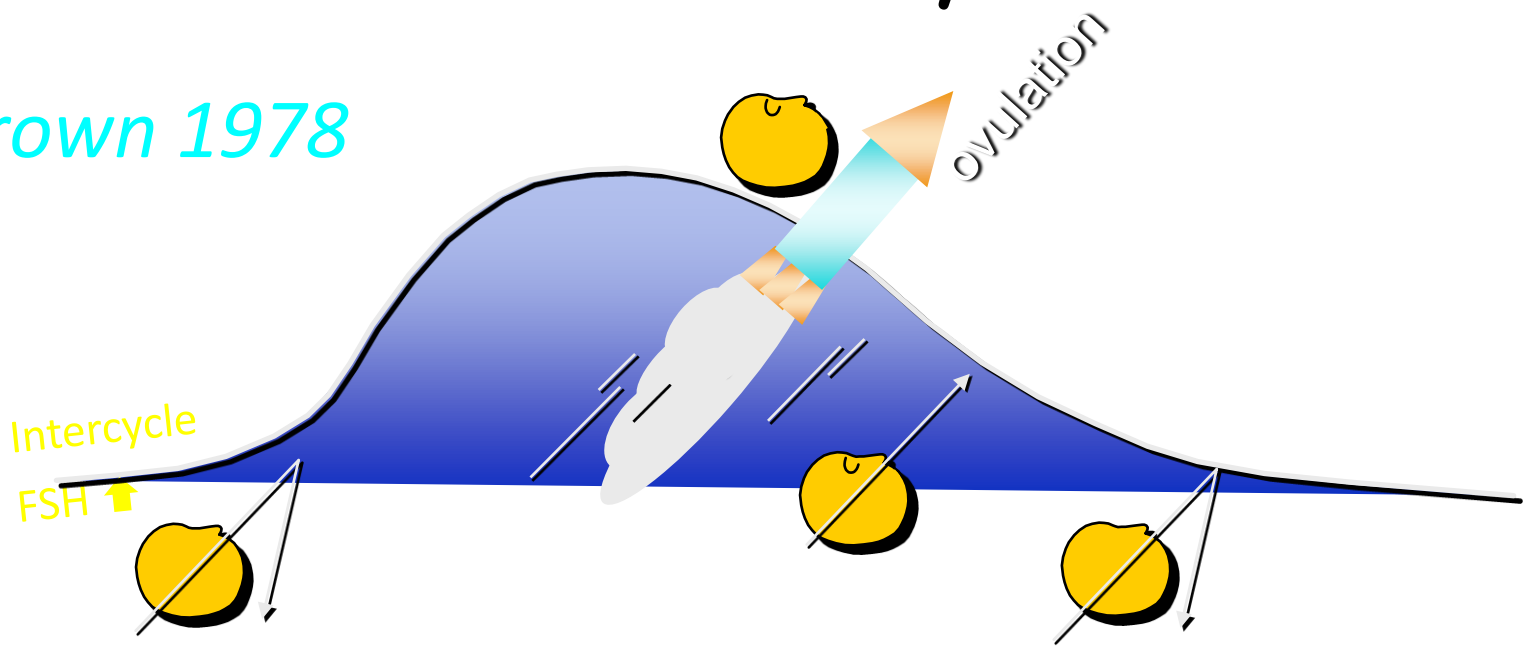
The rationale

- ↑ Number of oocytes available (↑ chance of fertilization)
- ↑ Steroid production (↑ chance of implantation)
- It may correct subtle ovulatory disorders, such as luteinized unruptured follicle syndrome, not detected with routine diagnostic studies

More exact time to ovulation and insemination can be determined

Synchronization of the menstrual cycle

Brown 1978



- inter-cycle ↑FSH is the marker for functional onset of ovarian cycle.
- Only those antral follicles which coincide with the inter-cycle rise in FSH can enter the final stages of follicular growth

Synchronization of the menstrual cycle

Controlling the timing of occurrence of inter-cycle increase in FSH :

- Timely use of E2 (2 mg estradiol valerate, starting 3 days before the onset of menses of the previous cycle.
- Short-term use of the OC pill for 7 to 21 days in the cycle preceding stimulation cycle.

Ovarian Stimulation Protocols

- Clomiphene citrate or similar drugs
- u-hMG or highly purified u-hMG
- Purified u-FSH or highly purified u-FSH
- Recombinant (r-FSH)
- Combinations

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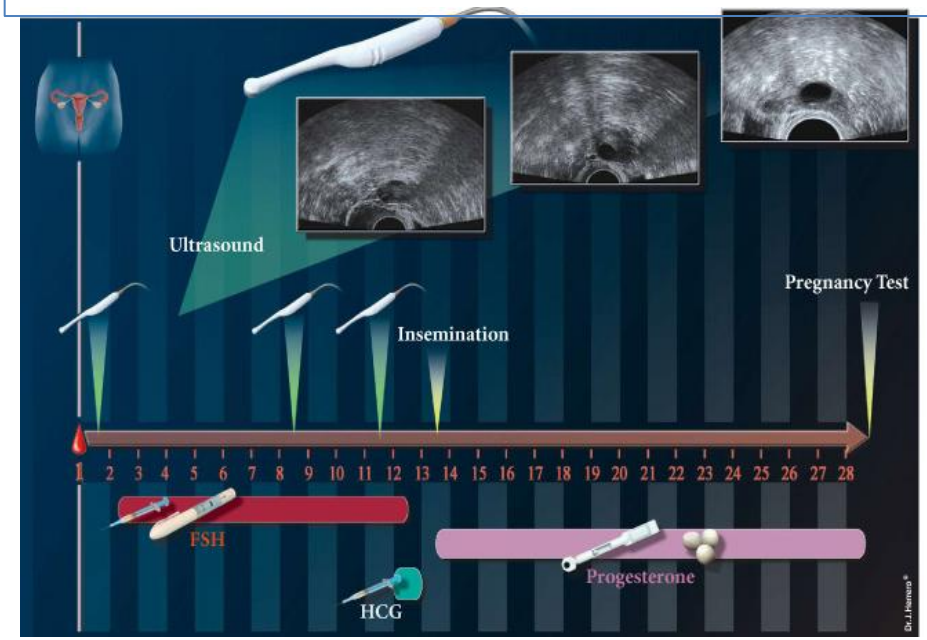
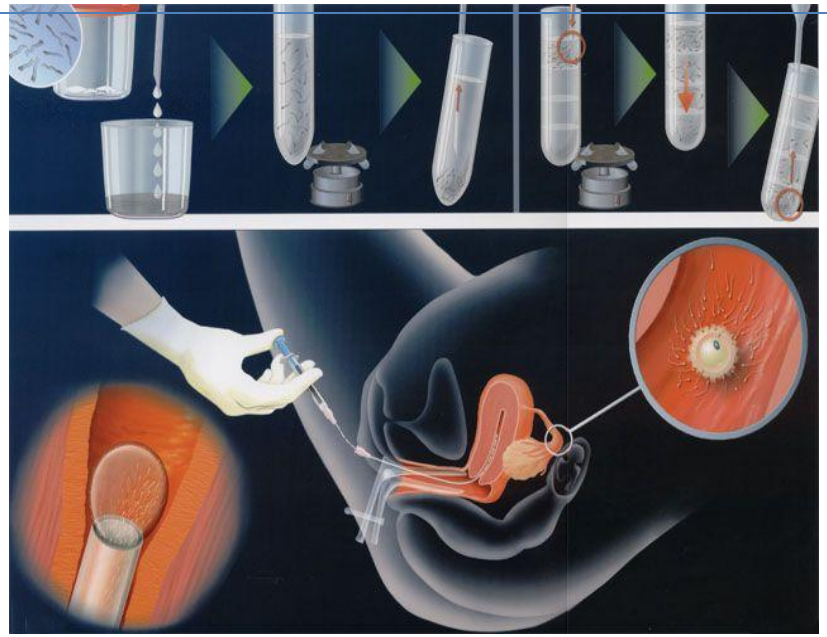
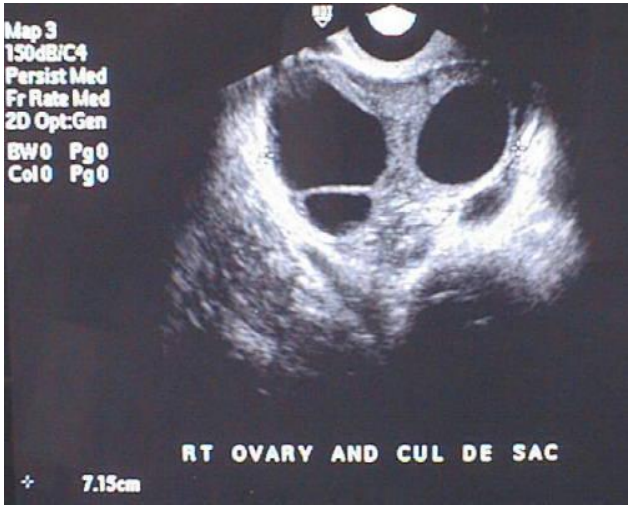
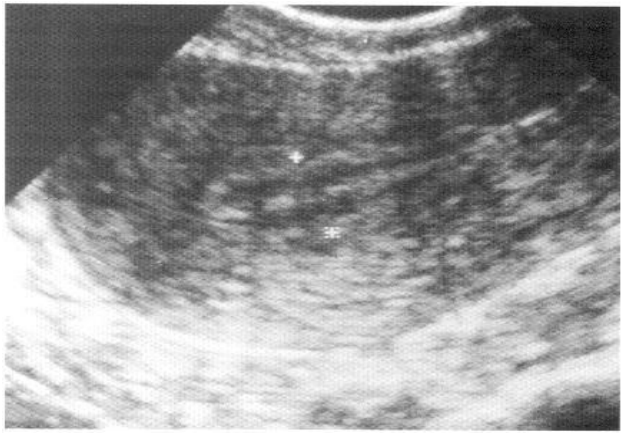




Monitoring ovarian stimulation





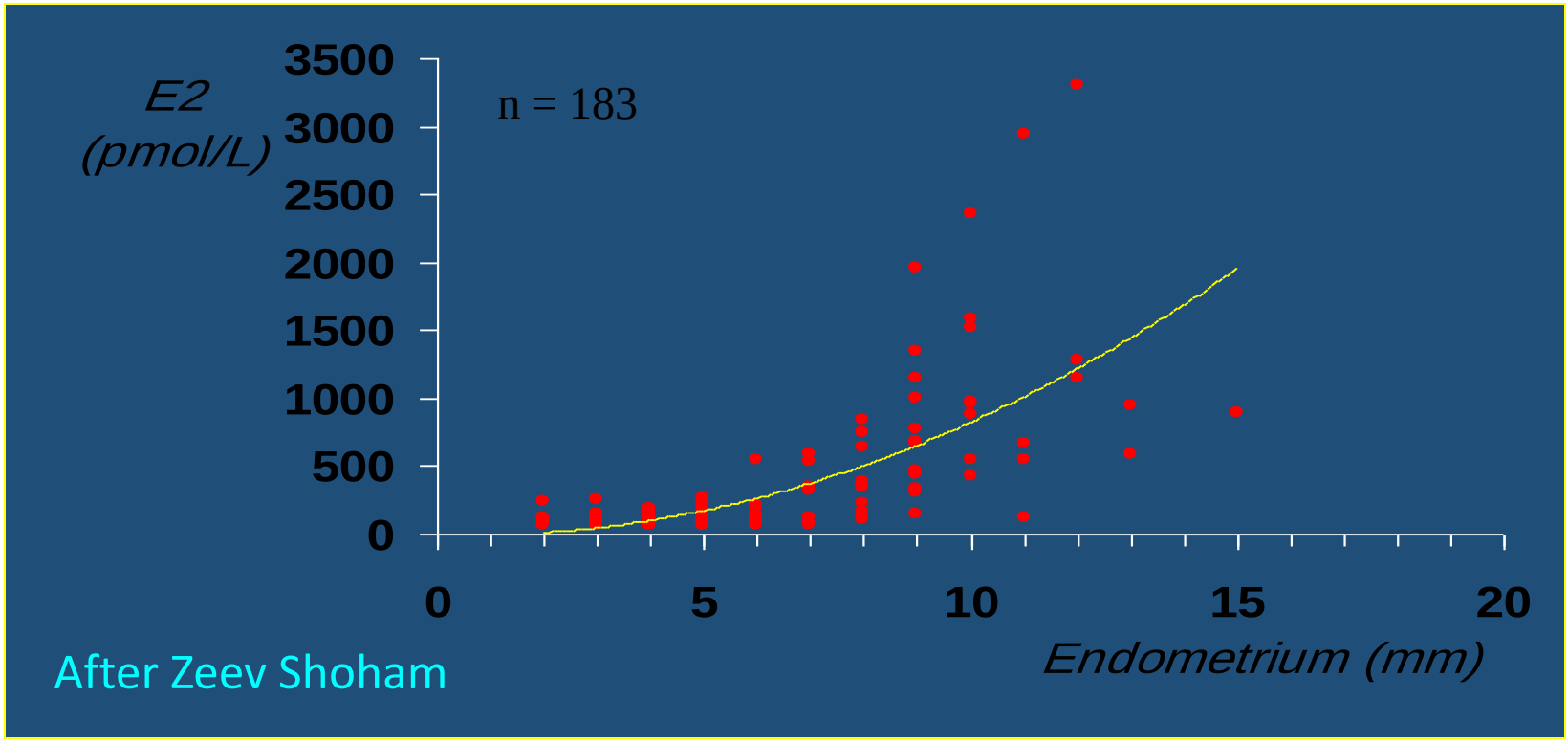
- Transvaginal ultrasound scanning :

. No. & size of follicles

. Pattern & thickness of endometrium

- Hormonal blood level (E2, FSH, LH)

Endometrial thickness & Monitoring ovarian stimulation



Correlation between E2 and endometrial thickness

Optimum ovarian stimulation For IUI

- 1 - 2 follicules with Ø 18 – 19 mm.
- Estradiol blood level :

  250-300 pgm / ml per ≥ 15 mm follicle.
- Endometrium ≥ 9 mm thick & trilaminar.
- IUI between Cycle D13 and D16.

Cancellation :

- ≥ 6 follicles ≥ 15 mm irrespective of E2 level
- Estradiol ≥ 1500 pg/ml.

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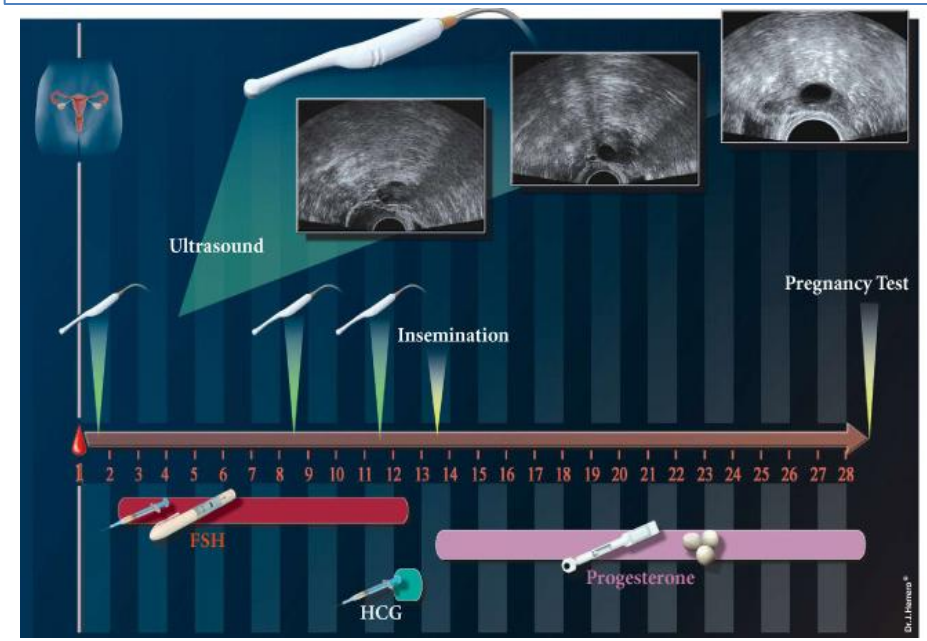
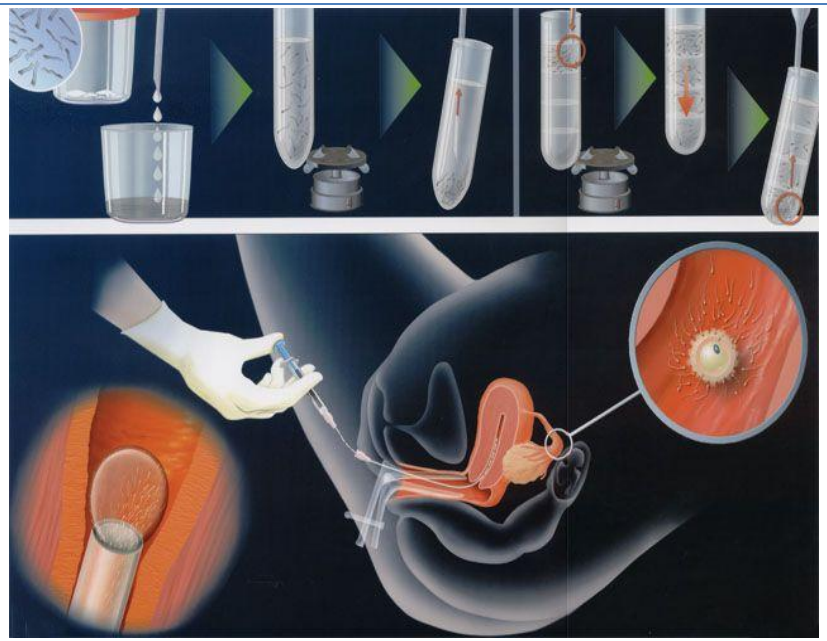
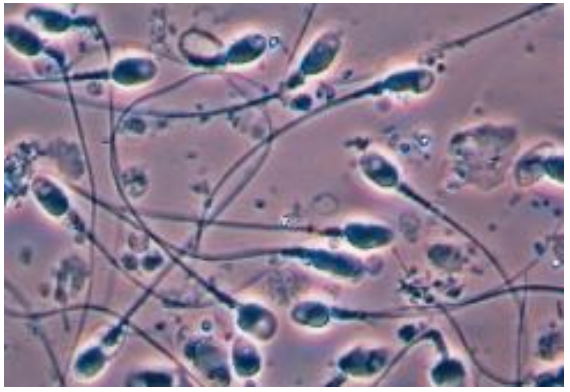




Sperm processing

- Simple Sperm wash
- Swim-up following sperm wash once or twice (Samples with an acceptable number of motile sperm (> 20 millions / ml)).
- Density gradient column separation (filtration in Percoll gradients, PureSperm or Isolate) (Poor quality semen samples) .



Sperm processing
Rationale

- **Concentration of progressively motile and morphologically normal** spermatozoa into a small volume of culture fluid.
- The washing procedures are necessary **to remove prostaglandins, infectious agents, antigenic proteins, non-motile spermatozoa, leucocytes and immature germ cells**
- This may enhance sperm quality by **decreasing the formation of free oxygen radicals** after sperm preparation. The final result is an improved fertilizing capacity of the sperm in vitro and in vivo.
- Many studies have shown that appropriate sperm processing may **reduce the risk of HIV, transmission through IUI and IVF/ICSI.**

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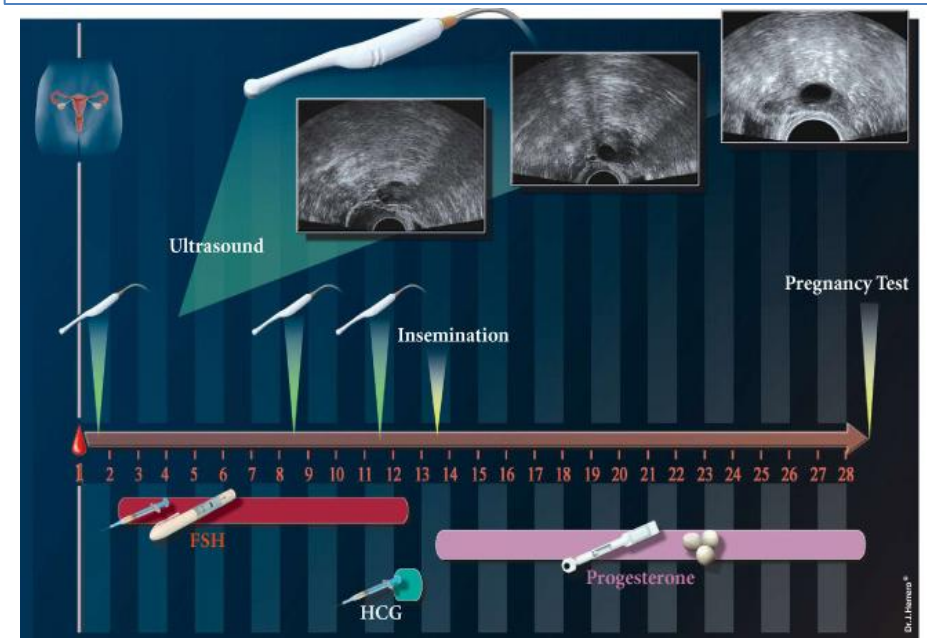
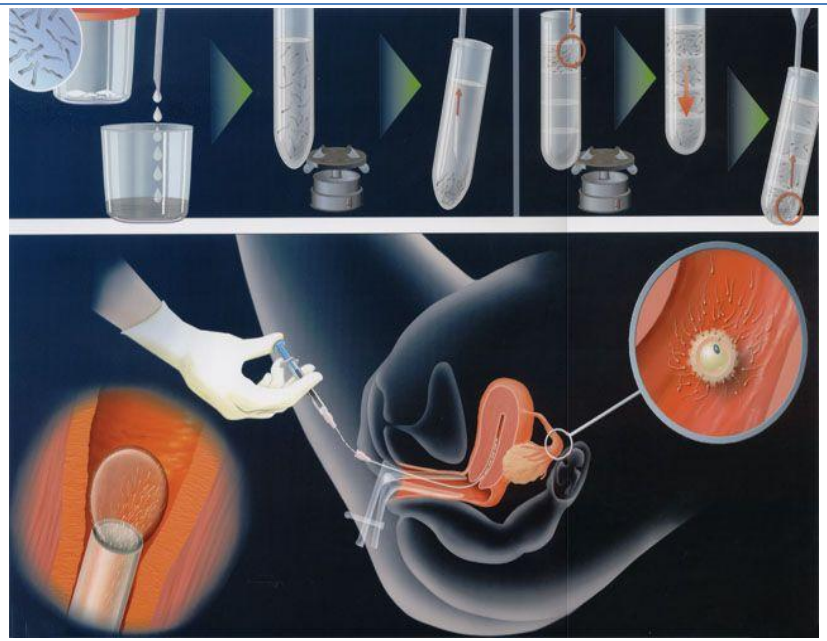




Timing and Frequency of IUI

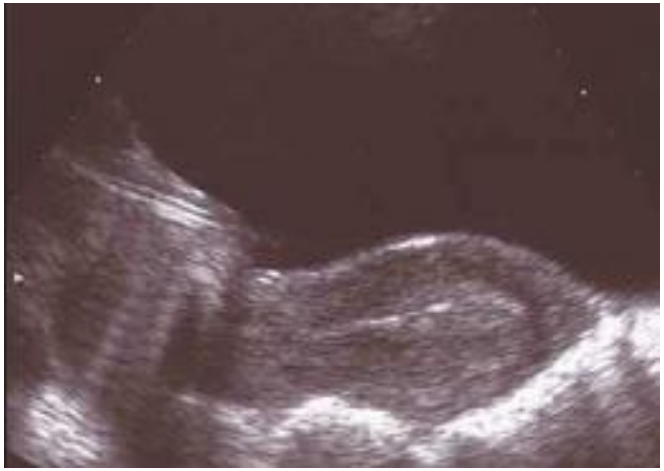
Fixed protocol:

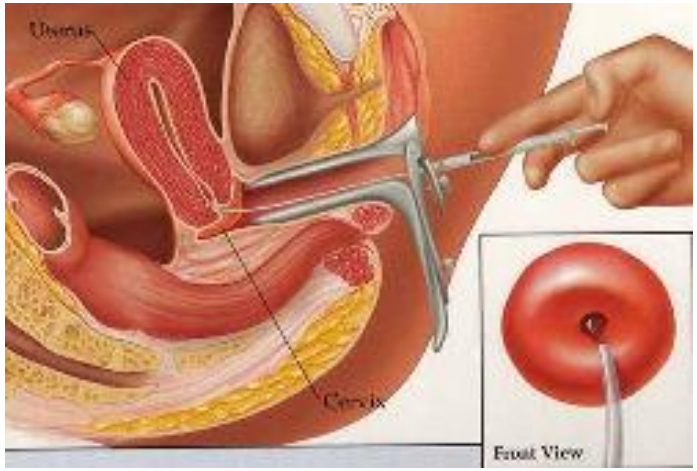
- Single insemination:
  36 – 40 hrs post – hCG
- double insemination:
  within 12 & 48 hrs post - hCG

Variable protocol:

- TVS 36 h post hCG: - Ovulated → single IUI
  - Not Ovulated → IUI at once
  → IUI 24 hrs later

IUI: Technique





- *Partially filled urinary bladder; lithotomy position & abdominal US*
- *Gently and atraumatically clean the cervix with saline soaked swab ⇨ introduce IUI catheter through cervix; no touch to fundus*
- *Slowly inject 0.3-.05 ml of processed semen*
- *Slowly withdraw catheter*
- A 10 minutes bed rest after IUI has a positive effect on PR.
- Intercourse within 12-18 hours of IUI.

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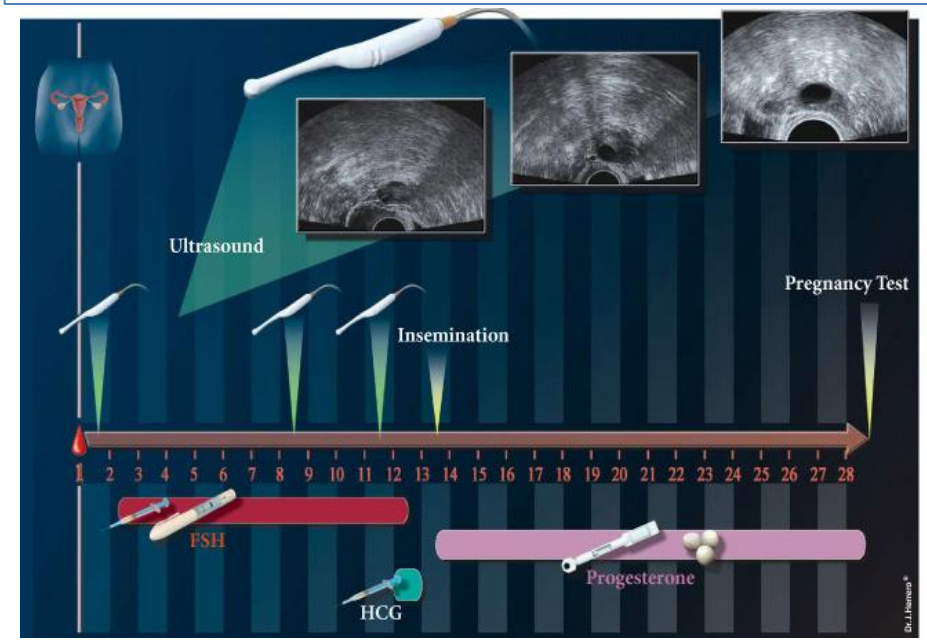
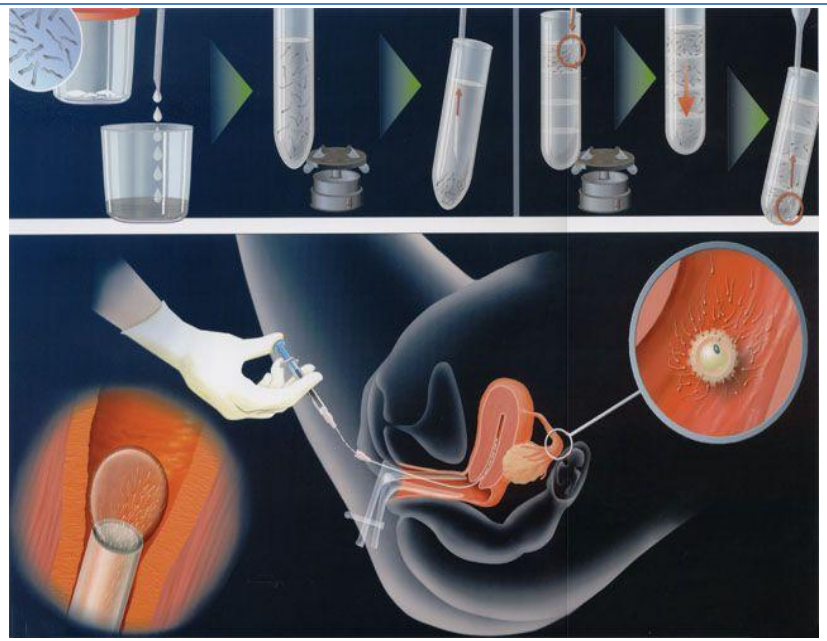
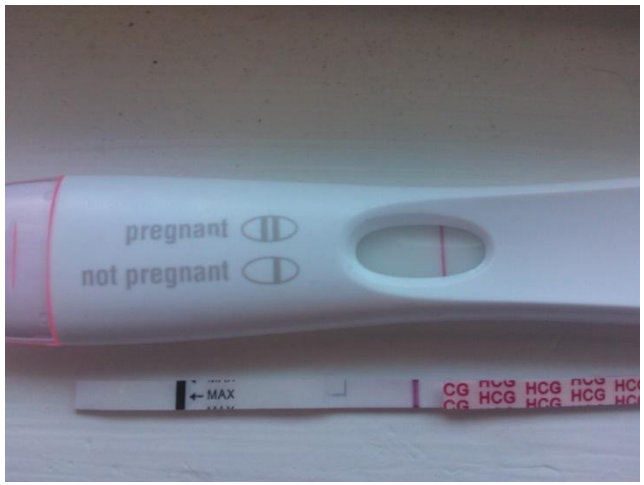




Luteal phase support

Progesteron suppositories 200 mg twice/day until pregnancy test and until 12° week of gestation in the case of pregnancy



Number of trials of IUI ?

Pregnancies resulting from IUI occur during early treatment cycles.

88% of pregnancies occur in the first three cycles of IUI and 95.5% within the first four cycles *(Morshedi M et al, 2003).*

Continued IUI beyond four trials

is not recommended

SUMMARY

- **IUI is relatively simple, non-invasive, cheap & easily repeatable.**
- **Careful selection of patient is important.**
- **There is good evidence in the literature in favor of IUI as a cost-effective treatment for unexplained and mild, moderate male factor sub fertility.**
- **Although it may take relatively more treatment cycles to achieve pregnancy, there are considerable advantages to the patient in terms of risk / benefit ratio and financial cost as compared with other ARTs.**
- **Failure of 4 - 6 trials of Gn. stimulated IUI in unexplained or mild male infertility, is an indication for IVF.**

IN VITRO FERTILIZATION
EMBRIO TRANSFER
IVF-ET

IVF-ET Patient Selection

- ✓ Tubal factor
- ✓ Severe male factor infertility
- ✓ Diminished ovarian reserve
- ✓ All other causes of infertility, after failing treatment with less invasive therapies (eg, ovulatory dysfunction, endometriosis, unexplained infertility)
- ✓ Ovarian failure (*donor eggs*)
- ✓ Uterine factor (if severe, gestational surrogacy may be needed in conjunction with IVF)

Severe Pelvic / Tubal factor

Structural abnormalities	Functional abnormalities
Adhesions	Abnormal peristalsis
Stenosis	Spasms
Terminal phimosis	
Deposition of fibrous tissue in the smooth muscular tunic of the tubal wall, with subsequent stiffening	
Alterations of the ciliary epithelium	

...caused by...

Pelvic inflammatory disease (PID), previous salpingitis (N.Gonorrhea, C. Trachomatis, TBC), Endometriosis, previous ectopic pregnancies, previous abdominal-pelvic surgery

Moderate-Severe male factor

Oligo- Astheno –Teratospermia

The patients can be candidated to IVF/ET or to ICSI on the grounds of the results of their spermiograms

Sperm count: > 1 million
Normal morphology: > 4%

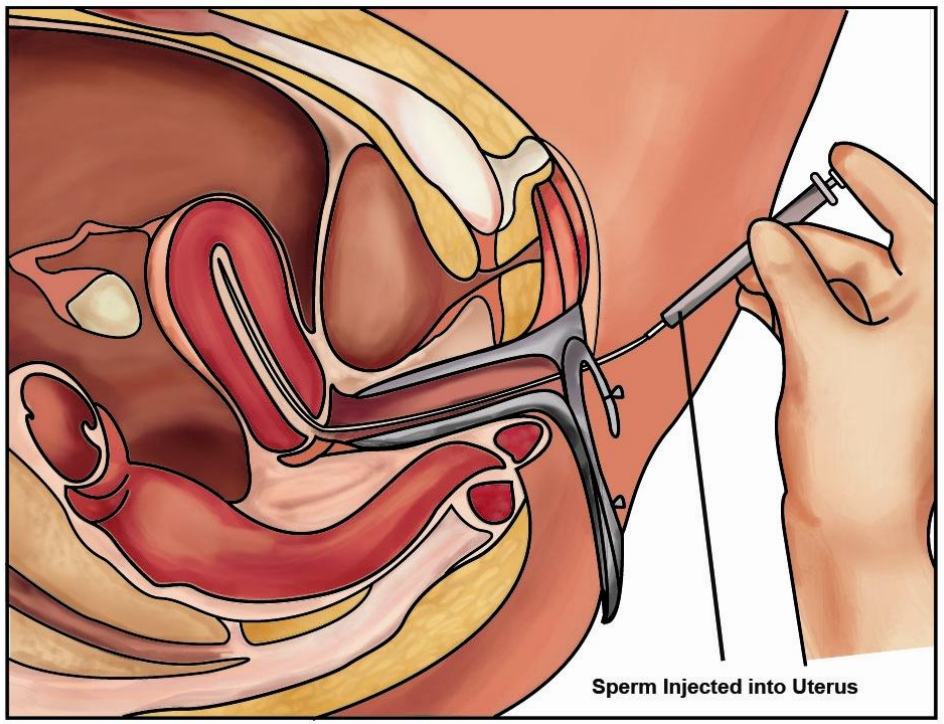
IVF/ET

Sperm count: < 1 million
Normal morphology: < 4%

ICSI

Failure of previous IUI cycles

After 3 to 6 IUI stimulated or unstimulated cycles the patients should be candidated to more advanced techniques of ART



IVF/ET Technical procedure

A regimen of gonadotropin stimulation induces multiple follicular maturation.
The oocytes are retrieved by transvaginal ultrasound-guided needle aspiration.

There are 5 basic steps in IVF/ET procedure, which include:

1. **Controlled ovarian hyperstimulation**
2. **Oocyte retrieval**
3. **In vitro fertilization**
4. **Embryo transfer**
5. **Luteal phase support**

1. Controlled ovarian hyperstimulation

Controlled ovarian hyperstimulation

is aimed at **2 main goals**:

- Control of the hypophysial activity (preventing untimely endogenous LH surge, premature ovulation as well as premature luteinisation of the follicles)

- Multifollicular recruitment: synchronous development of multiple follicles

1. Controlled ovarian hyperstimulation

Ovarian hyperstimulation is performed through the combined administration of GnRH agonists (GnRH-a) or antagonists (GnRH-ant) and r-FSH, according to

3 possible protocols.

- Long Protocol (Down Regulation)
- Short Protocol (Flare up Protocol)
- Ultrashort protocol

- The first two are based on the administration of GnRH-a, while the latter is based on the administration of GnRH-ant.

1. Controlled ovarian hyperstimulation

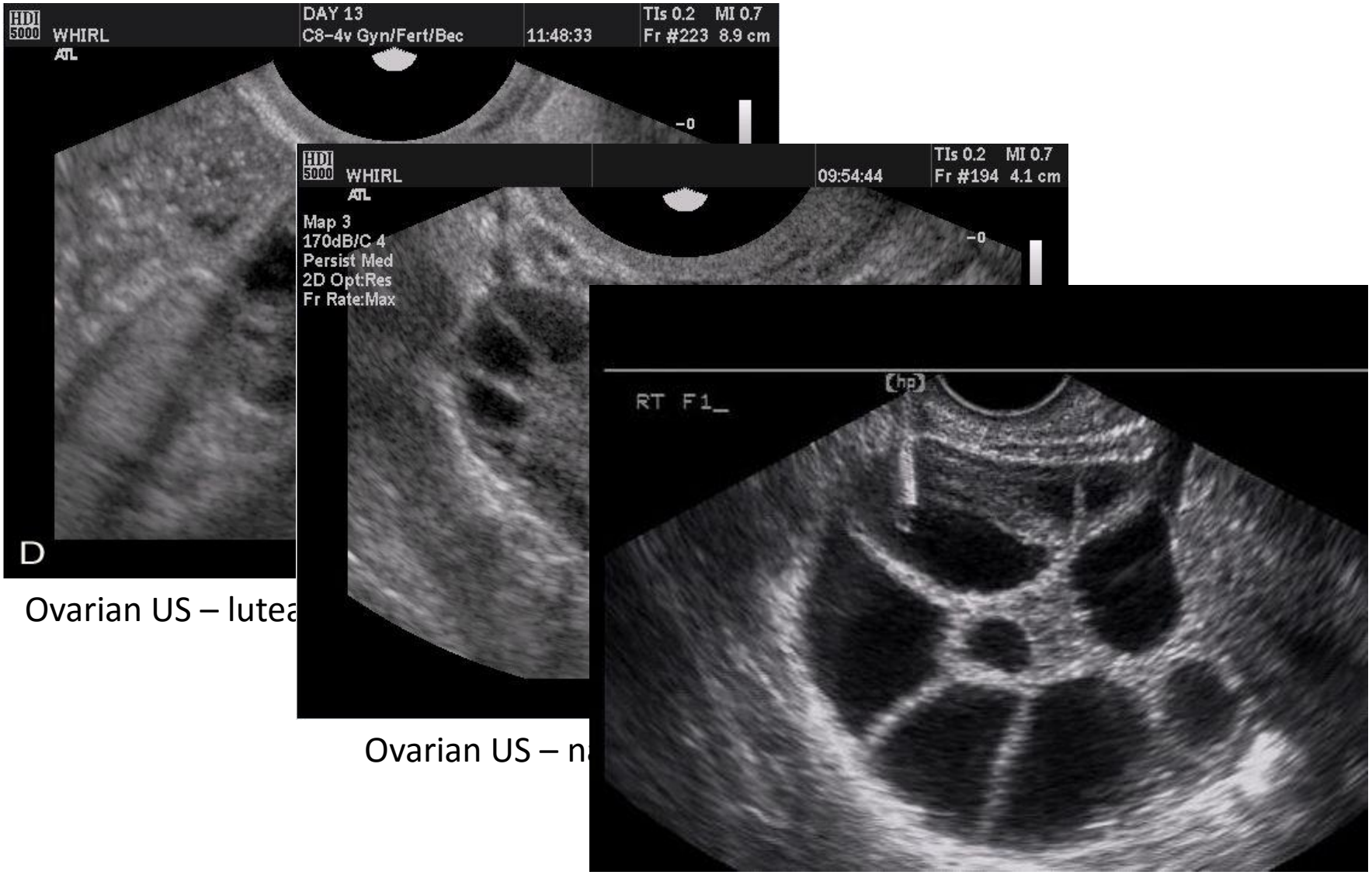
- "Long protocols" involve starting medications in the menstrual cycle before the IVF cycle.
- "Short protocols" refer to a regimen in which medications are started at the time of the natural menstrual cycle.

Triggers for ovulation

When the ovarian follicles are judged to be mature (two or more follicles with a mean diameter of 18 mm or more and a serum estradiol level of 200 pg/mL [734 pmol/L] per codominant follicle), a trigger is administered to initiate the ovulatory cascade.

Urinary or recombinant hCG preparations

Ultrasonographic aspect of the ovary



Ovarian US – lutea

Ovarian US – n

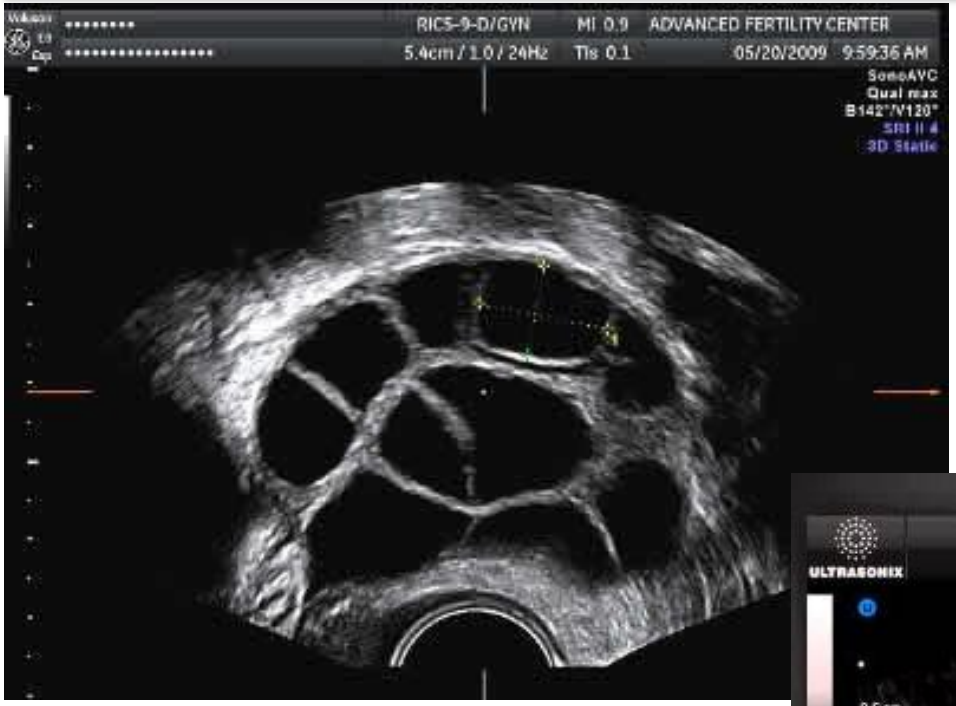
Ovarian US – stimulated multifollicular ovary

2. Oocyte retrieval

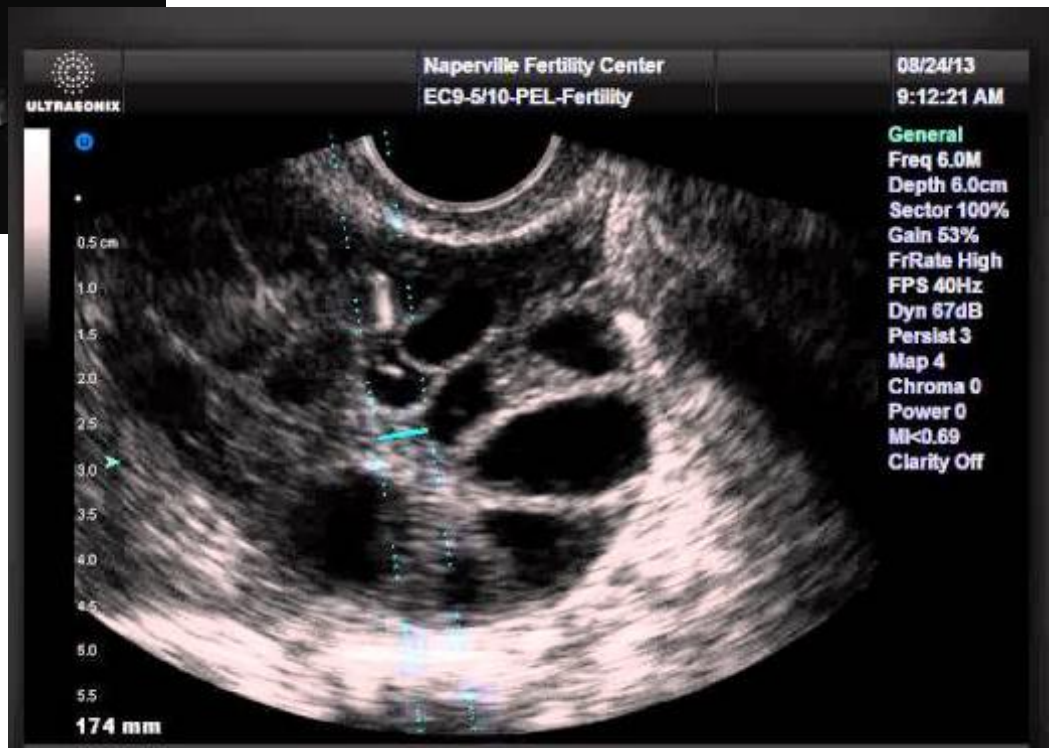
- 34 to 36 hours after trigger for ovulation
- analgesia/anesthesia

(intravenous propofol, conscious sedation or regional block)

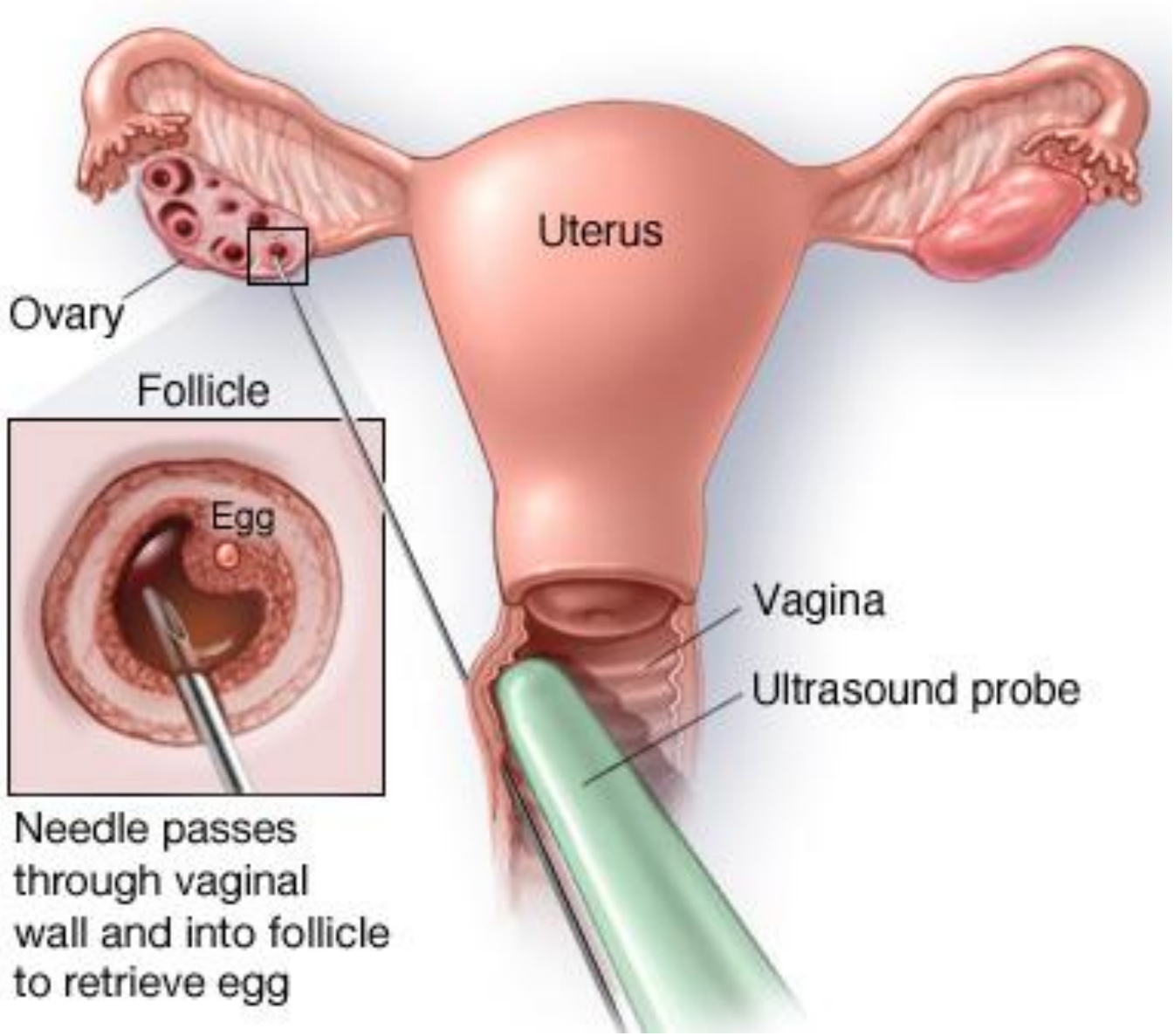
Follicle aspiration



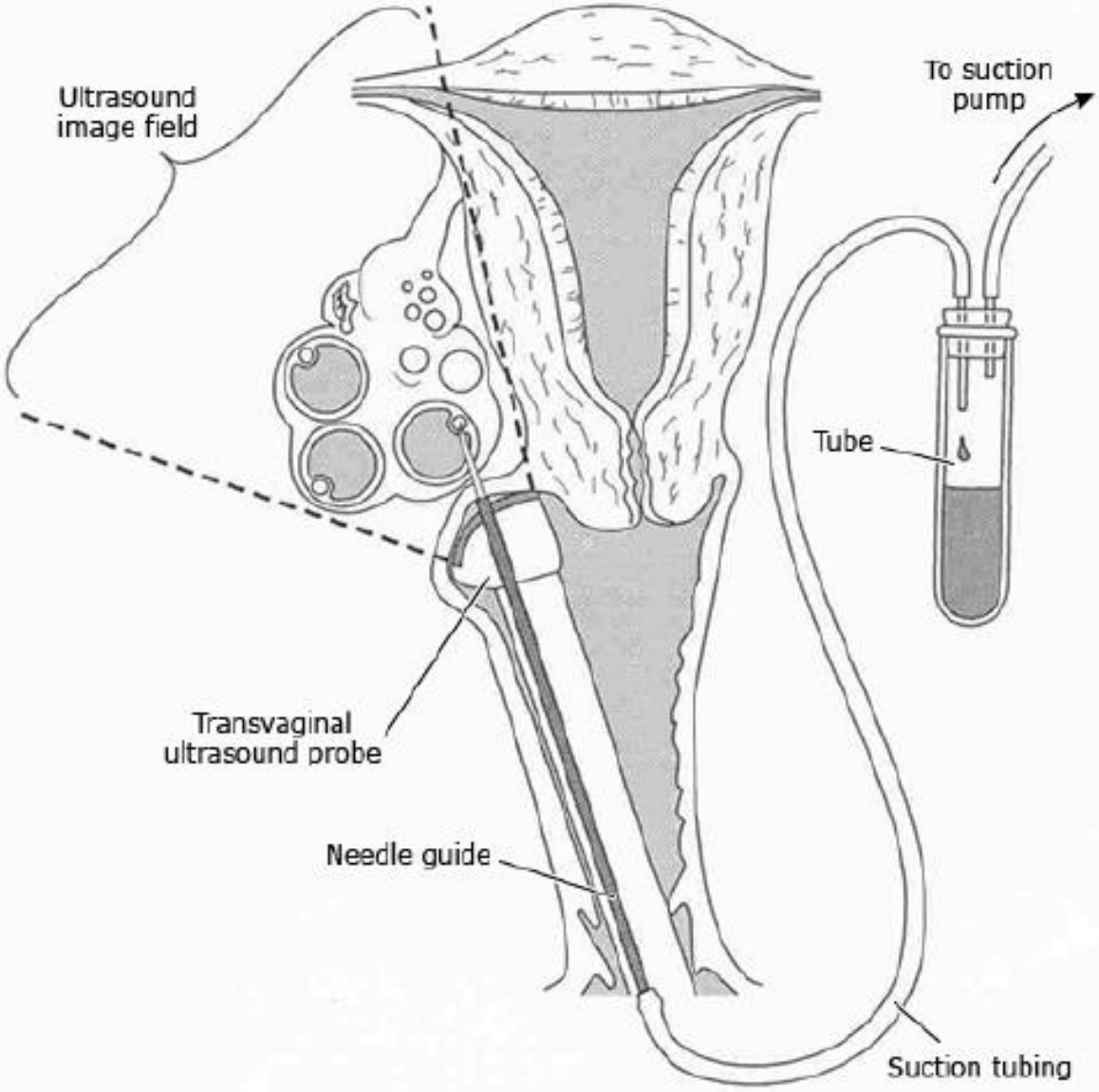
direct ultrasonographic visualization



Follicle aspiration

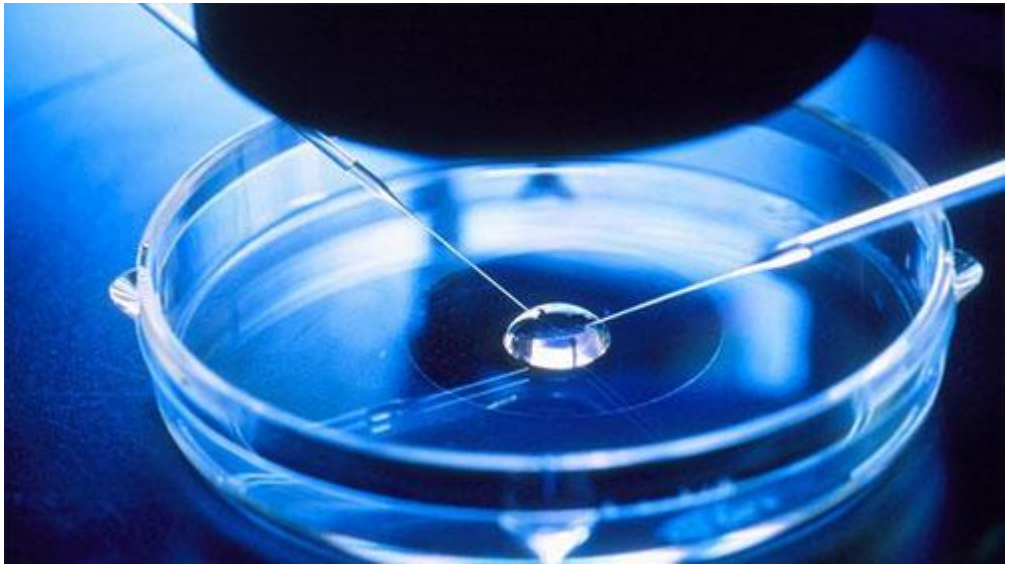


Follicle aspiration



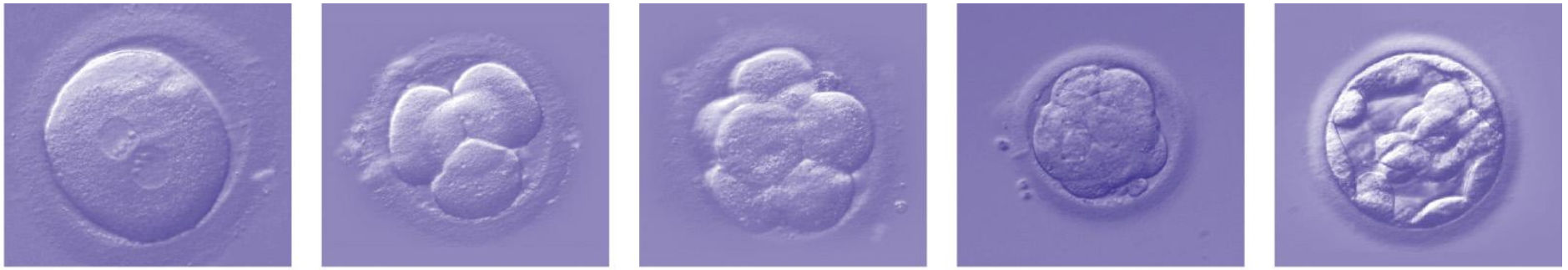
A needle is introduced sequentially into each follicle and the follicular contents are aspirated.
From one to more than 40 oocytes may be retrieved, though **10 to 20** is typical

3. In vitro fertilization



To achieve fertilization, recovered oocytes are mixed with spermatozoa in a small volume of culture medium based on human fallopian tubal fluid and incubated at 37°C. The optimum number of hours for incubation of sperm and oocytes has not been determined

Embryo management



Day 1
Fertilisation

Day 2
4 cell

Day 3
8 cell

Day 4
Morula

Day 5
Blastocyst

Fertilization of the oocyte is confirmed by observing two pronuclei within the zygote about 17 hours after insemination.

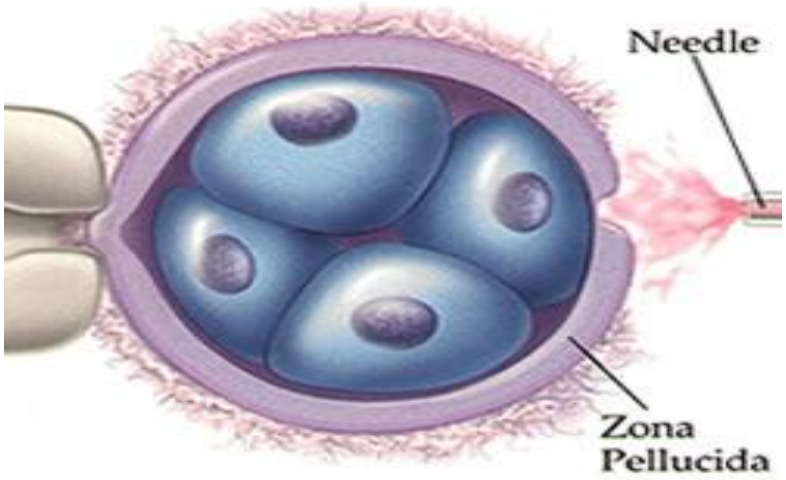
The individual cells of each embryo ("blastomeres") divide every 12 to 14 hours.

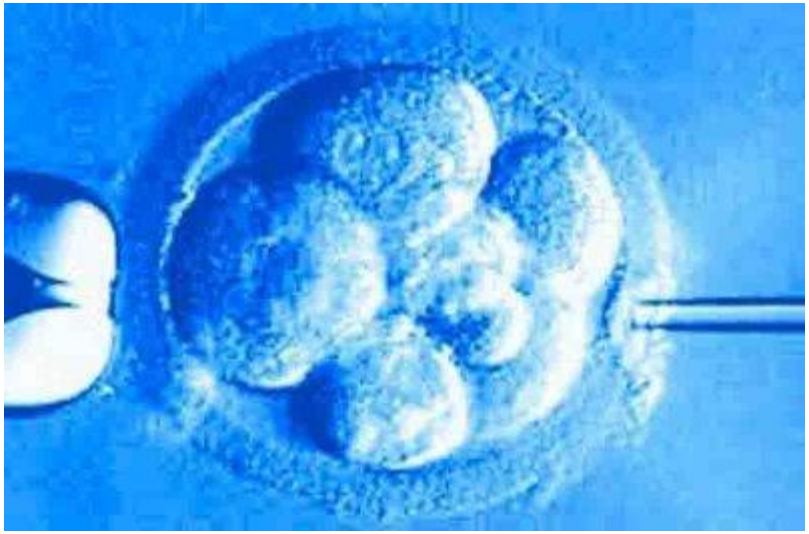
Embryos between days 2 and 4 are called "cleavage stage embryos."

The blastocyst stage is reached by about day 5 after retrieval.

Implantation is expected by day 7 after egg retrieval, so transfer should take place prior to this time.

Assisted hatching

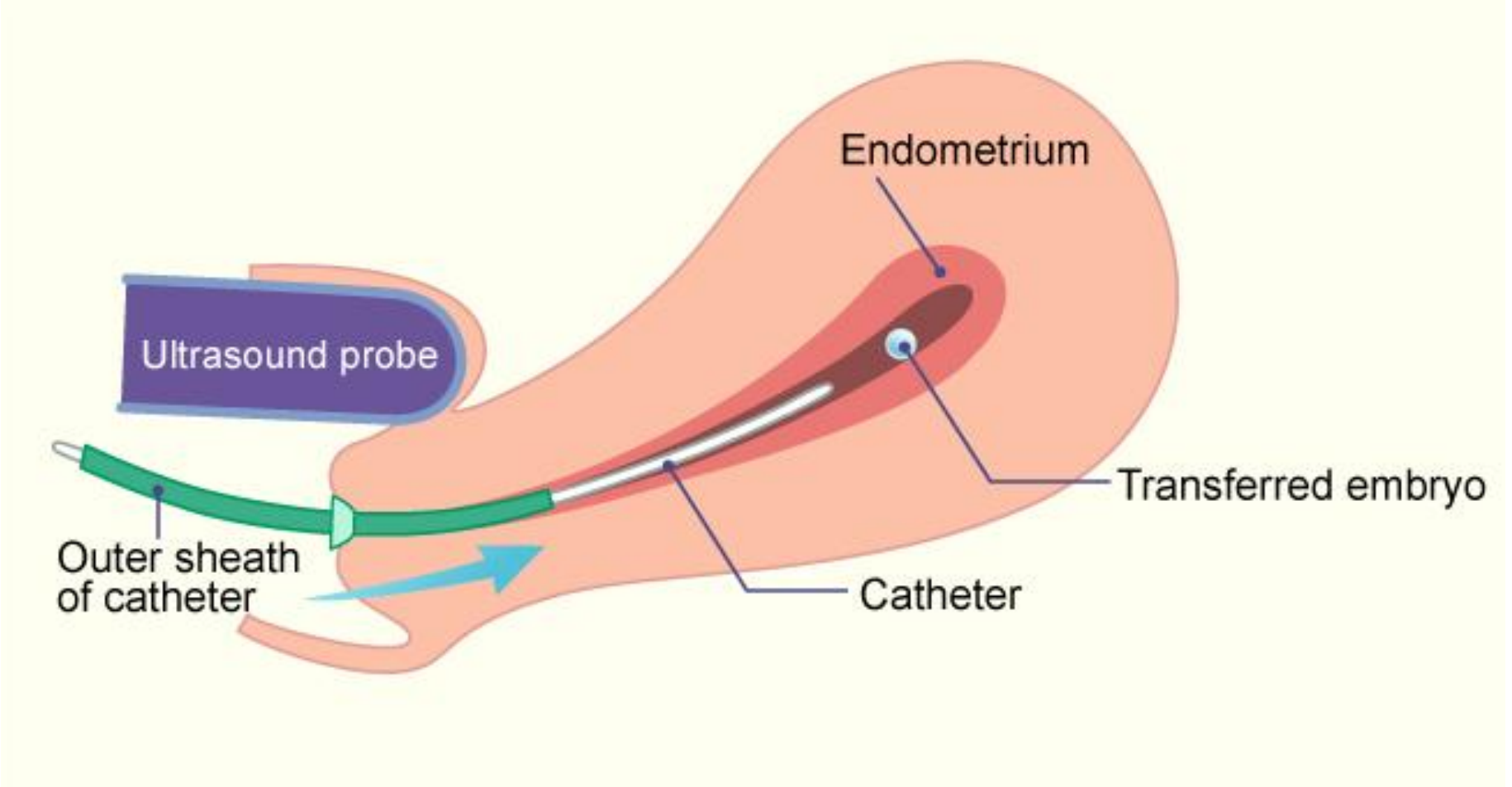




The zona pellucida around the day 3 embryo is mechanically or chemically opened to assist the embryo in hatching from the zona about three days later.

Its value is controversial

4. Embryo transfer



4. Embryo transfer

- Embryos can be inserted into the uterus using a catheter via the cervix
- The type of catheter (soft versus hard) and other aspects of the transfer technique, such as use of ultrasound guidance, can affect the success of transfer.
- However, ***operator experience*** remains a major factor in the success of the procedure.

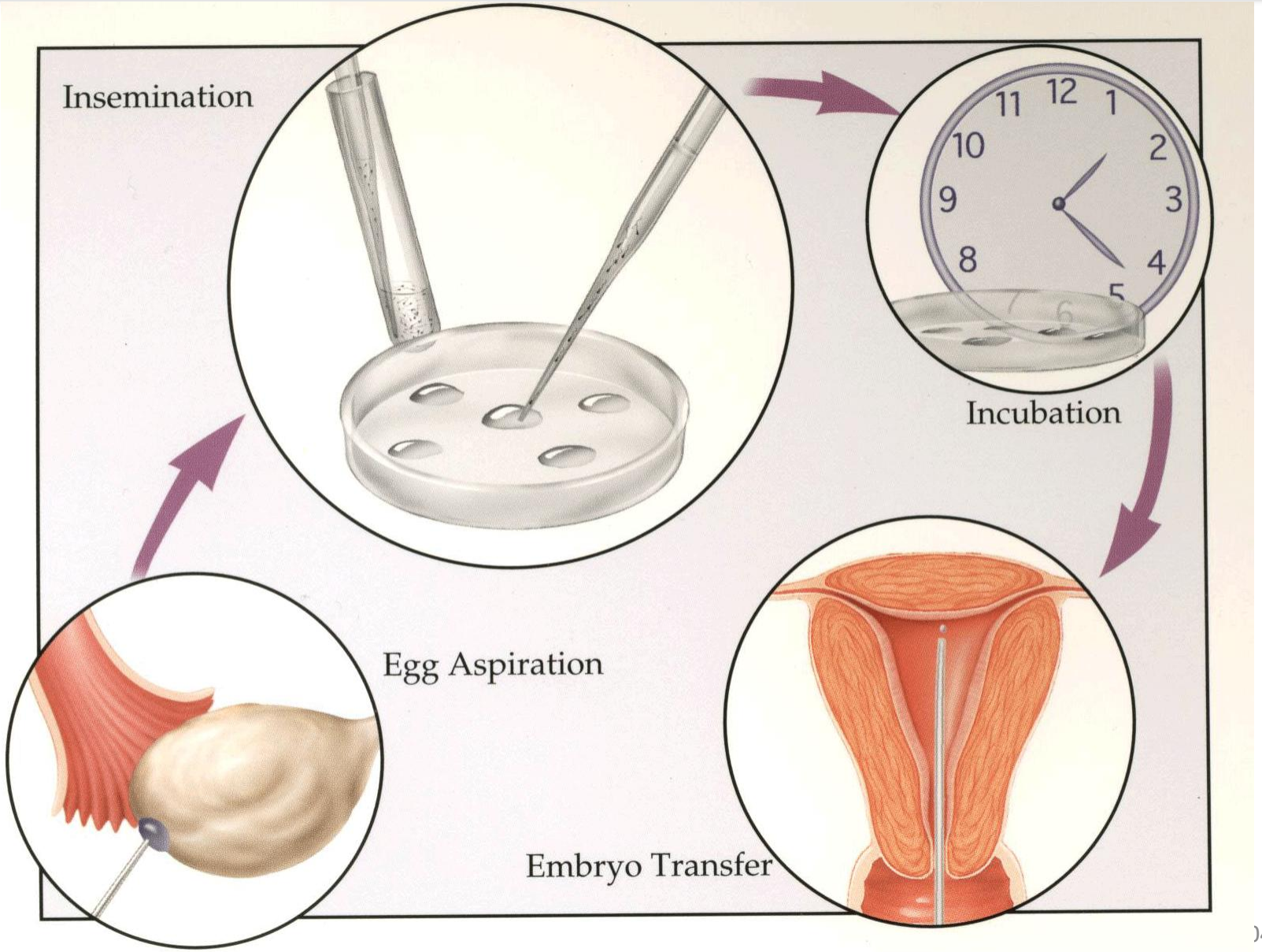
4. Embryo transfer

- Most programs transfer embryos to the uterus about **3 days after egg retrieval** (4-8 cell, cleavage stage)
- **Day 5 transfer** (blastocyst stage) is the next most common time for transfer.

  Advantages of blastocyst stage transfer:

  - the ability to perform PGD

IVF



5. Luteal phase support

- Since the drugs administered during controlled ovarian hyperstimulation (GnRH-a and GnRH-ant), inhibit gonadotropins' release from the pituitary, **the endogenous support of the luteal phase is insufficient**.

- Thus, **exogenous progesterone is given** after embryo transfer to optimize endometrial receptivity for embryo implantation.

- It may be given by **intramuscular** injections (50 or 100 mg) or various **vaginal** formulations during the luteal phase and continued until gestational week 8 or 10.

Cryopreservation

- Embryos in excess of those that can be safely transferred can be cryopreserved for future use.

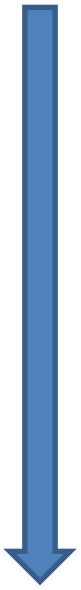
- There is no scientific basis for a maximum duration of storage

Factors associated with success

- Younger maternal age:

  % of cycles using fresh embryos from nondonor oocytes *that resulted in a live birth* by maternal age was:

< 35 yrs	→ 40.7 %
35 – 37 yrs	→ 31.3 %
38 – 40 yrs	→ 22.2 %
41 – 42 yrs	→ 11.8 %
> 42 yrs	→ 3.9 %



Factors associated with success

- Adequate ovarian reserve
  - follicle stimulating hormone (FSH)
  - estradiol

help predict the success of the IVF procedure.

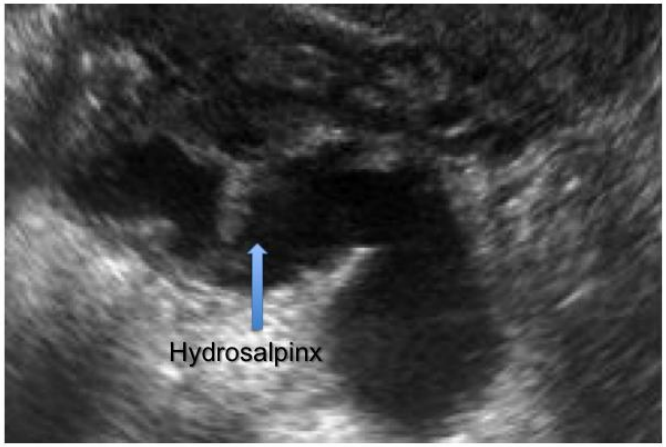
A high day 3 level is a poor prognostic factor.

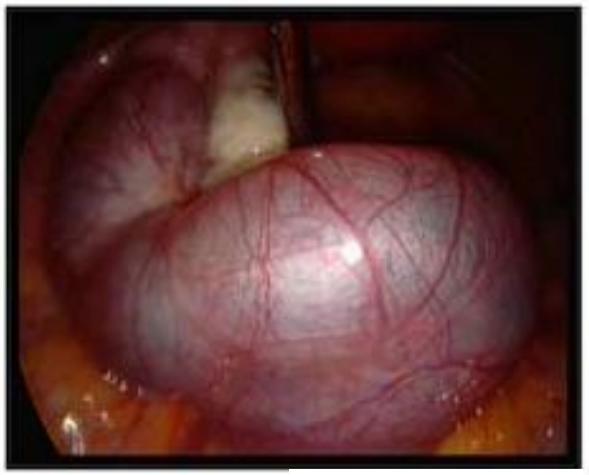
Factors with variable association with success

- Leiomyoma
- Endometriosis / endometrioma
- Previous pregnancy history
- Prevuious unsuccessfull IVF cycle (until approximately the fourth IVF cycle)
- Obesity
- Acquired / inherited trombophilia
- Endometrial thickness

Factors negatively affecting IVF success

- **hydrosalpinx:** hydrosalpingeal fluid may impair establishment of a successful pregnancy by negatively impacting the transferred embryo or endometrial receptivity.





- **cigarette smoking:** reduced ova retrievement

INTRACYTOPLASMATIC SPERM INJECTION
ICSI

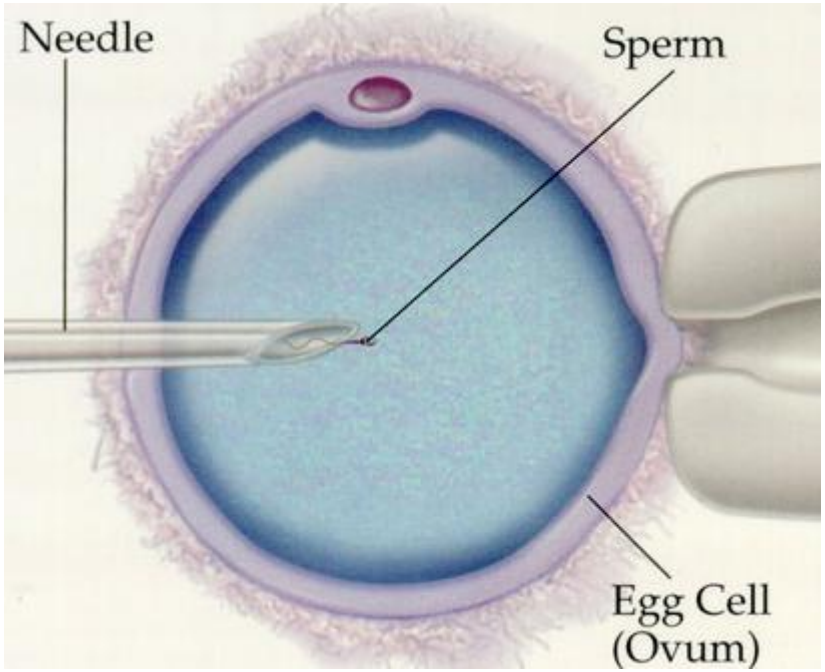
ICSI: indications

- Severe male factor infertility (Sperm count: < 1 million; Normal morphology: < 4%)
- Obstructive azoospermia due either to congenital absence of the vas deferens or to prior vasectomy AND nonobstructive azoospermia from sperm maturation arrest (microsurgical or percutaneous aspiration from the epididymis or the testes)
- Antisperm antibodies in the semen
- Oocytes matured in vitro or cryopreserved.
- Previous failed IVF/ET attempts

ICSI: technical procedure

- ICSI involves immobilizing sperm in polyvinylpyrrolidone, or by crushing the tail, then aspirating a single spermatozoon into a microneedle.

- The oocyte, which has been stripped of its surrounding cumulus mass, is stabilized with a holding pipette, and the sperm is injected directly into the ooplasm.



ICSI: rationale

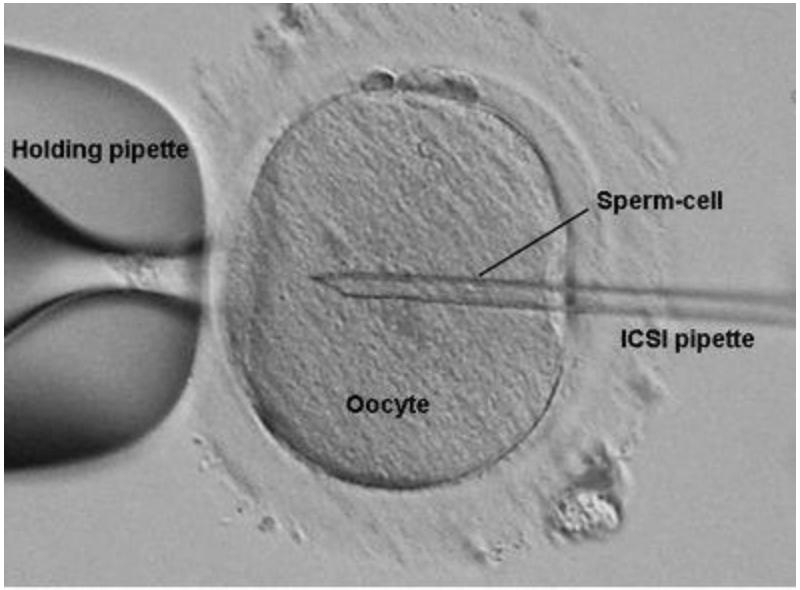
- Fertilization is documented the following morning by the presence of the male and female pronuclei.

- **ICSI** restores fertilization and pregnancy rates to those comparable to conventional IVF in couples with **severe male factor infertility**.

ICSI: rationale

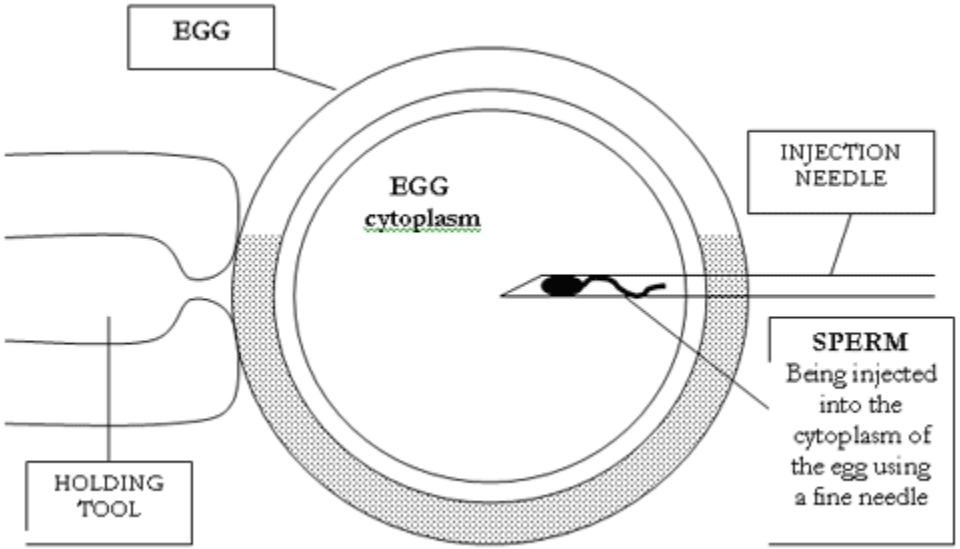
- It **overcomes** possible spermatic, immunologic, oocytary interference to the fertilization process obtained through conventional ICSI.

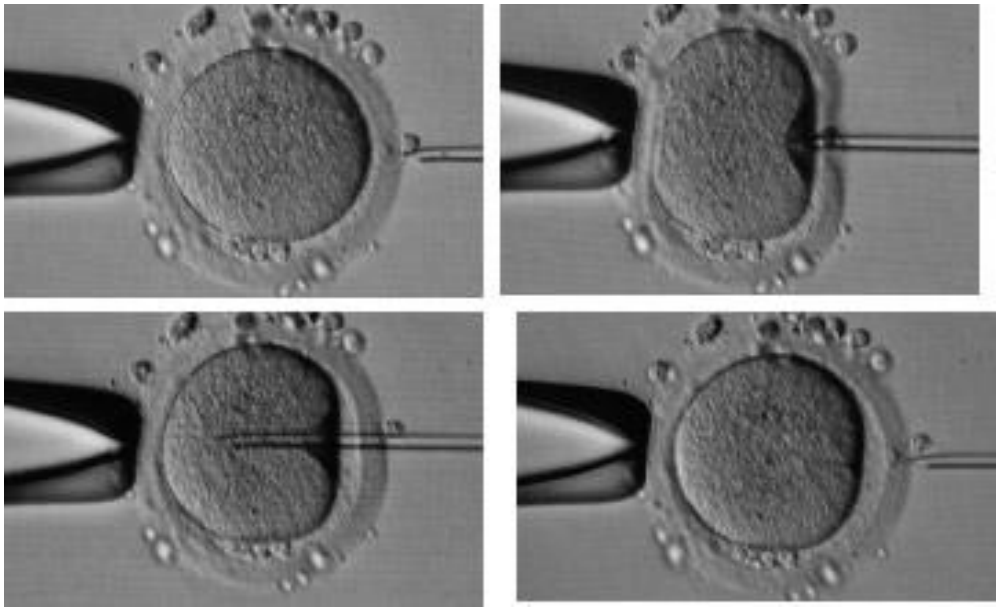
However it remains an **invasive** technique, that can threaten embryo development.



ICSI

ICSI


EGG
EGG
cytoplasm
INJECTION NEEDLE
SPERM
Being injected into the cytoplasm of the egg using a fine needle
HOLDING TOOL



Assisted Reproductive Technologies

Gamete intrafallopian transfer (GIFT)
A laparoscope is used to aspirate one or more mature oocytes from ovarian follicles and then transfer the oocytes and sperm to the fallopian tube.
GIFT, although more invasive than IVF, may be an appropriate choice in patients who, for religious or personal reasons, do not wish to have embryos in the laboratory. It is also appropriate for those who have failed donor insemination or require laparoscopy for other reasons. The success rate is similar to those with IVF.
Zygote intrafallopian transfer (ZIFT) or tubal embryo transfer (TET)
This procedure involves placement of fertilized eggs (zygotes) or embryos into the fallopian tube.
ZIFT is analogous to GIFT in that laparoscopy is needed to place the zygotes in the fallopian tubes. Whereas overall success rates are similar to IVF, ZIFT may offer some advantages to patients with difficult trans-cervical embryo transfer, uterine abnormalities (such as those caused by DES exposure), or recurrent failture with standard IVF

Pregnancy rates

	< 36 years	Total
Per cycle (IVF & ICSI)	22,1%	19,5%
Per pick-up	23,7%	21,1%
Embryo transfert	25,6%	22,9%
FIVET (per Embryo transfert)	25,6%	22,7%
ICSI (per Embryo transfert)	25,6%	23,1%

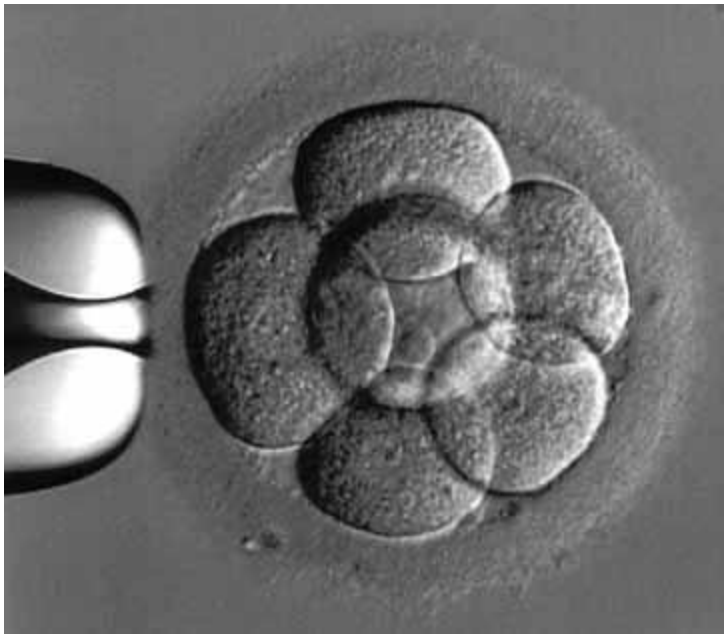
Disadvantages

- high cost
- need for drug administration
- need for invasive procedures
- increased rate of multiple gestation
- slight increase in fetal complications

THIRDY PARTY REPRODUCTION

THIRDY PARTY REPRODUCTION

- Egg donation
- Sperm donation
- Surrogacy
  - Gestational carrier
  - Traditional Surrogacy
- Embryo donation

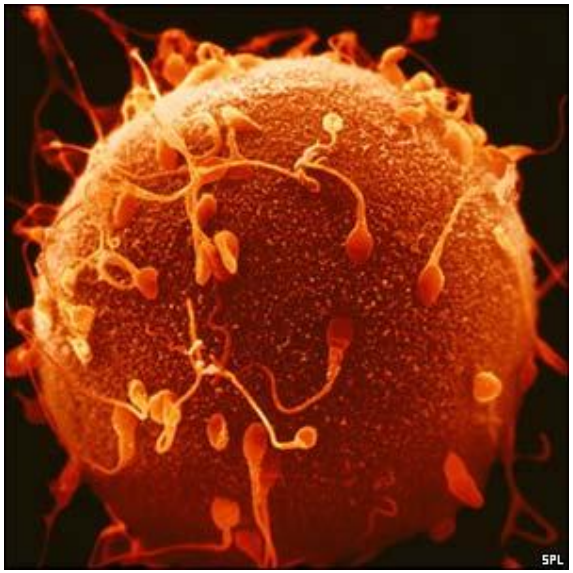


EGG DONATION: INDICATIONS

- Ovarian Failure.
- Poor egg quality.
- Recurrent IVF failure.
- Recurrent pregnancy loss
- Genetic defects precluding normal pregnancy.

EGG DONATION: THE PROCESS

- The process involves IVF.
- The resulting offspring will carry genetic material of the *donor* and the *male partner*.



EGG DONATION: THE PROCESS

- Donor and recipient cycles are *synchronized*.
- Eggs taken from the donor after *ovarian stimulation*.
- Eggs are fertilized with *recipient partner's sperm*.
- Embryos transferred to the uterus of a *hormonally primed recipient*.

EGG DONATION: THE PROCESS

- Donor
  - Synchronize cycle with recipient
  - Ovarian stimulation
  - Egg retrieval
- Recipient
  - Synchronize cycle with donor
  - Preparation of the uterus
  - Fertilization
  - Embryo transfer

SPERM DONATION

- Widely used for almost 50 years
- Known or unknown donors
- Frozen in liquid nitrogen
- Sperm banks offer sperm from qualified donors
- Web sites offer ability to choose the traits of the donors

SPERM DONATION

- Sperm is placed into the woman's uterus at ovulation (IUI)
- Sperm donation or sperm from several ejaculations can be pooled and concentrated
- Sperm can be retrieved from the epididymis or the testis using microsurgery

SURROGACY

- Two types:
  - Egg donor surrogacy
  - Gestational surrogacy

- Surrogate may be relative, friend, or paid stranger