In the name of God

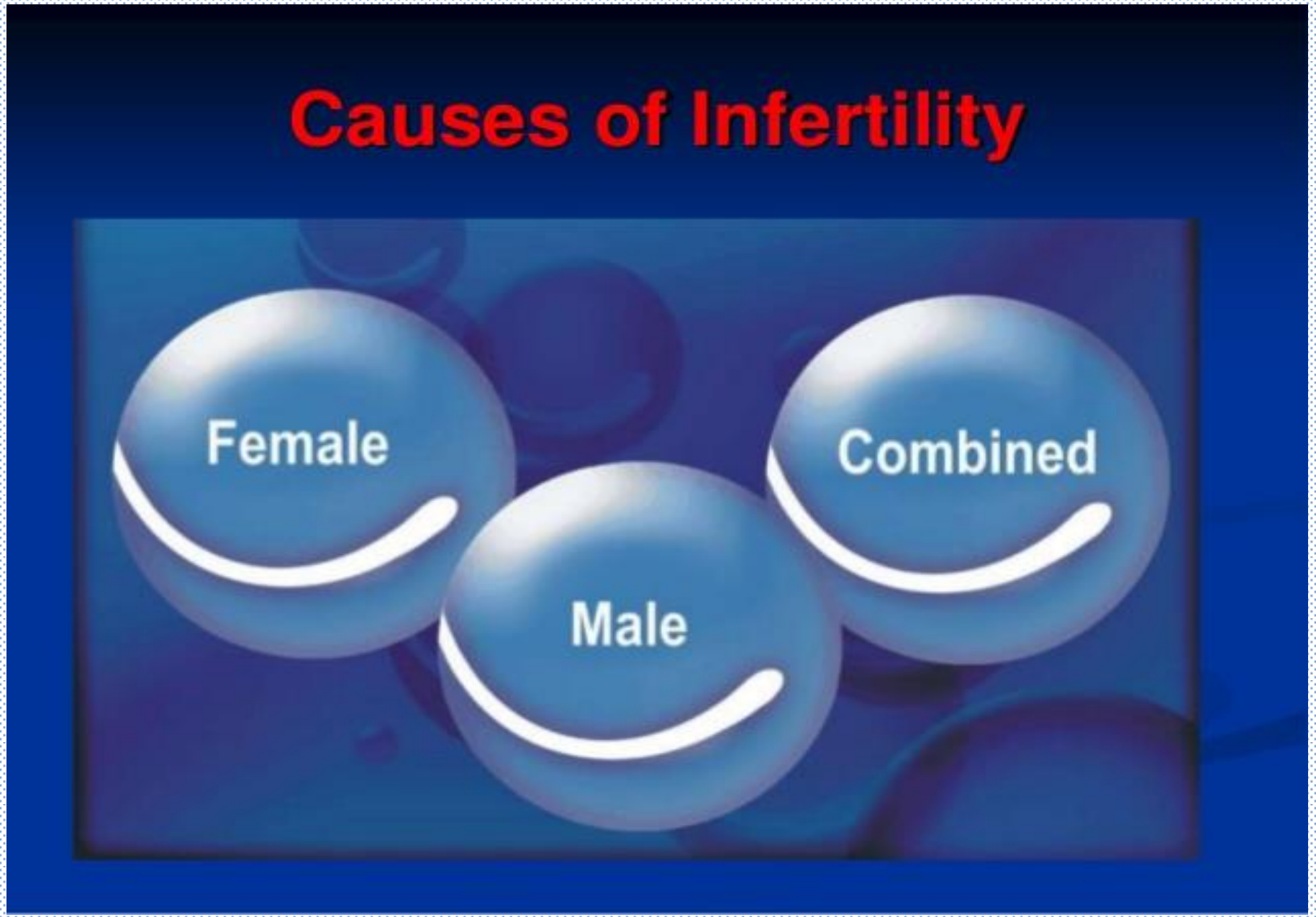
Investigation of infertile couple

Dr. N. Navali

Fellowship of infertility

- diagnostic evaluation for infertility is indicated for women who fail to achieve a successful pregnancy after **12 months** or more of regular unprotected intercourse
- Since approximately 85% of couples may be expected to achieve pregnancy within that interval without medical assistance, evaluation may be indicated for as many as 15% of couples.

- Earlier evaluation is warranted after six months of unsuccessful efforts to conceive in women **over age 35 years** and also including , but not limited to, the following:
  - **History of oligo - or amenorrhea**
  - **Known or suspected uterine/tubal/peritoneal disease or stage III–IV endometriosis**
  - **Known or suspected male subfertility**
- Where applicable, evaluation of both partners should begin at the same time.


Causes of Infertility
Female
Male
Combined

ETIOLOGY

- In a study of 8500 infertile couples done by the World Health Organization (WHO) The most common identifiable female factors which accounted for 81 percent of female infertility, included:
- Ovulatory disorders (25 percent)

  Endometriosis (15 percent)

  Pelvic adhesions (12 percent)

  Tubal blockage (11 percent)

  Other tubal abnormalities (11 percent)

  Hyperprolactinemia (7 percent

Evaluation

- Successful reproduction requires proper structure and function of the entire reproductive axis, including hypothalamus, pituitary gland, ovaries, fallopian tube, uterus, cervix, and vagina.

- To assess this axis, the infertility evaluation comprises eight major elements:
- (a) history and physical examination;
- (b) semen analysis;
- (c) sperm-cervical mucus interaction (postcoital testing);
- (d) assessment of ovarian reserve;
- (e) tests for occurrence of ovulation;
- (f) evaluation of tubal patency;
- (g) detection of uterine abnormalities; and
- (h) determination of peritoneal abnormalities.

The Most Important Factor in the Evaluation of the Infertile Couple Is: History

Relevant history includes the following:

- Duration of infertility and results of any previous evaluation and treatment
- Menstrual history (age at menarche , cycle length and characteristics, presence of molimina , and onset/severity of dysmenorrhea)
- Pregnancy history (gravidity, parity , pregnancy outcome, and associated complications)
- Previous methods of contraception
- Coital frequency and sexual dysfunction

- Past surgery (procedures, indications and outcomes), previous hospitalizations , serious illnesses or injuries , pelvic inflammatory disease , or exposure to sexually transmitted infections
- Thyroid disease, galactorrhea , hirsutism , pelvic or abdominal pain, and dyspareunia
- Previous abnormal pap smears and any subsequent treatment

- Current medications and allergies
- Family history of birth defects, mental retardation, early menopause, or reproductive failure or compromise
- Occupation and exposure to known environmental hazards
- Use of tobacco, alcohol, and recreational or illicit drugs

Physical examination should document the following:

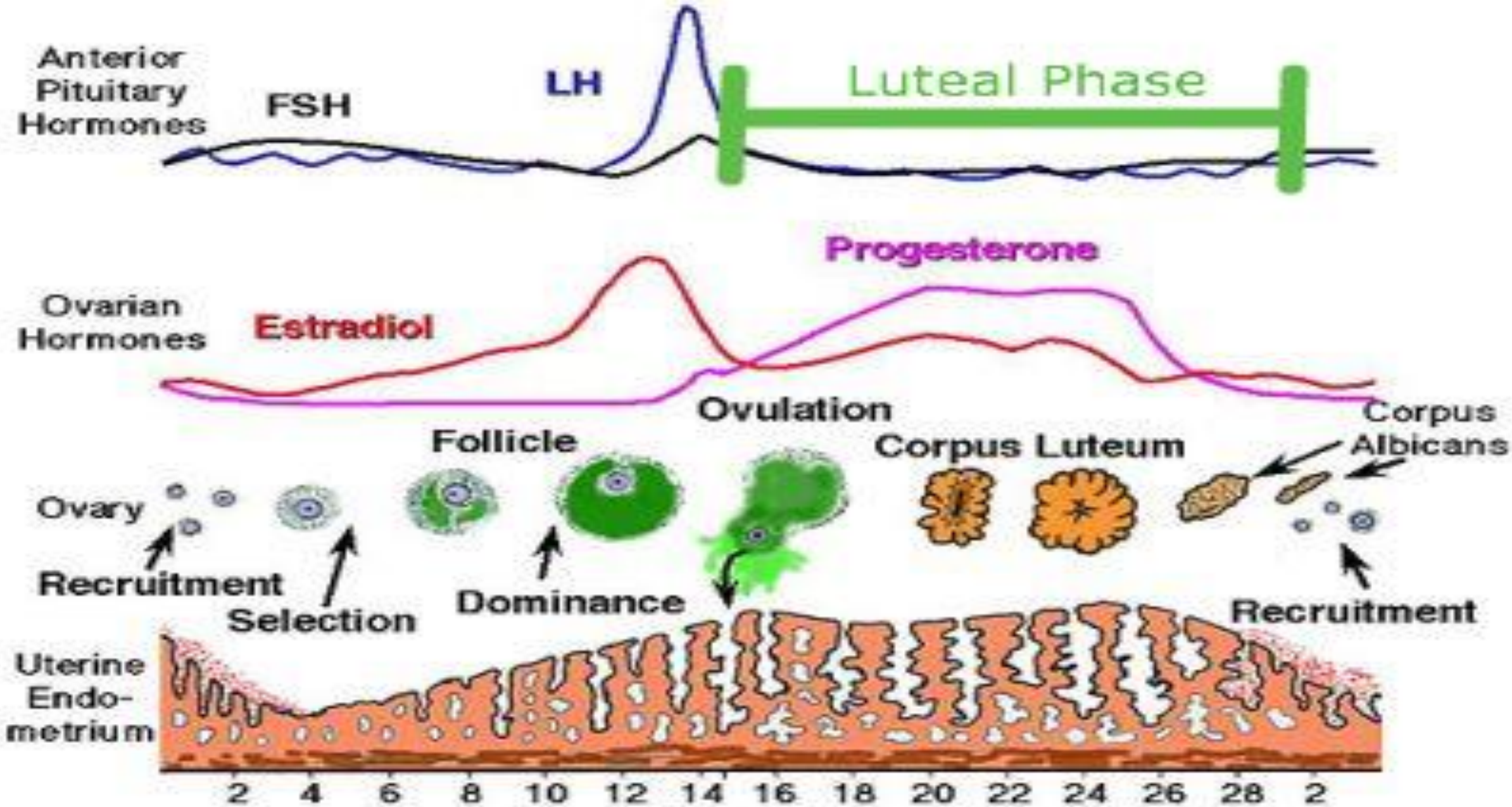
- Weight, body mass index (BMI),blood pressure, and pulse
- Thyroid enlargement and presence of any nodules or tenderness
- Breast secretions and their character
- Signs of androgen excess
- Vaginal or cervical abnormality, secretions, or discharge
- Pelvic or abdominal tenderness, organ enlargement, or masses
- Uterine size, shape, position, and mobility
- Adnexal masses or tenderness
- Cul-de-sac masses, tenderness, or nodularity

1- Confirmation of Ovulation

- **A- Menstrual history** may be all that is required.
- In most ovulatory women, menstrual cycles are regular and predictable, occurring at intervals of 25–35 days, exhibiting consistent flow characteristics, and accompanied by a consistent pattern of moliminal symptoms (breast tenderness, dysmenorrhea, bloating).
- Patients with abnormal uterine bleeding, oligomenorrhea, or amenorrhea generally do not require specific diagnostic tests to establish a diagnosis of anovulation.

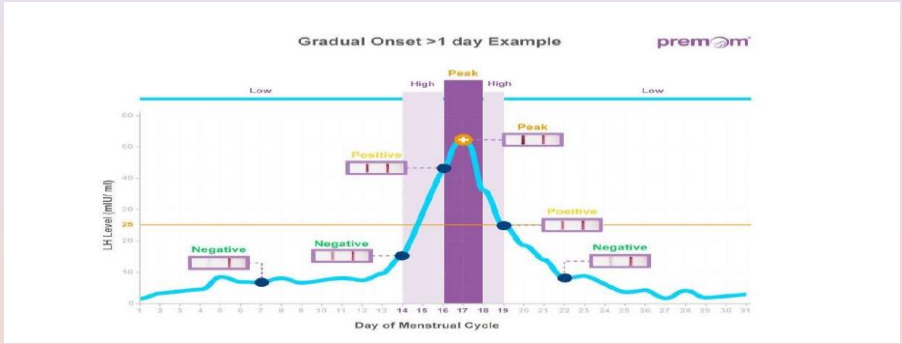
Serum Progesterone

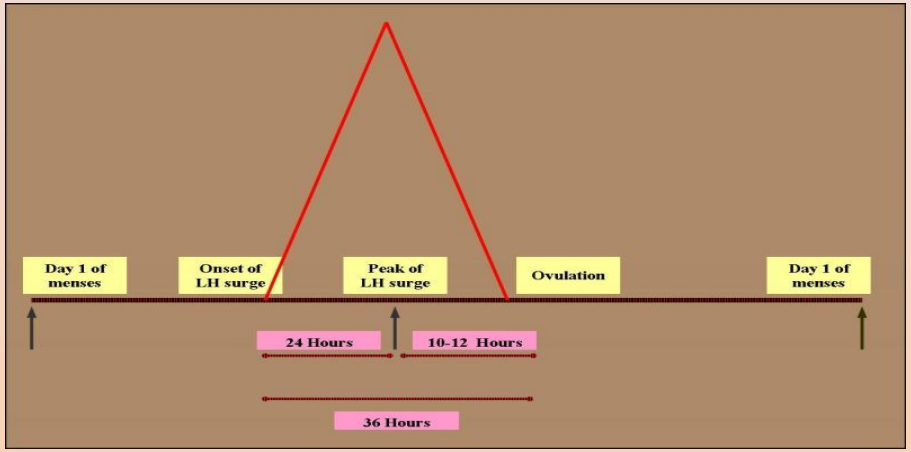
- Serum progesterone is ***reliable***, if obtained at ***appropriate time***, approximately *1 week before expected onset of next menstruation* rather than on any one specific day of menstrual cycle
- Progesterone concentration more than *3 ng/mL* is presumptive evidence of ovulation
- Although ***higher threshold value*** have been used commonly as a measure of ***quality of luteal phase***, it is not reliable
- because corpus luteal progesterone secretion is pulsatile and ***serum concentration may vary up to sevenfold within few hours***


Anterior Pituitary Hormones
FSH
LH
Luteal Phase
Progesterone
Ovarian Hormones
Estradiol
Ovulation
Follicle
Corpus Luteum
Corpus Albicans
Ovary
Recruitment
Selection
Dominance
Recruitment
Uterine Endo-metrium
2 4 6 8 10 12 14 16 18 20 22 24 26 28 2

D- Urinary luteinizing hormone (LH)

- Determinations using various commercial ‘‘ovulation predictor kits’’ can identify the midcycle LH surge that precedes ovulation by one to two days.
- Urinary LH detection provides indirect evidence of ovulation and helps to define the interval of greatest fertility: (**the day of the LH surge and the following two days**)





B- Serial basal body temperature (BBT)

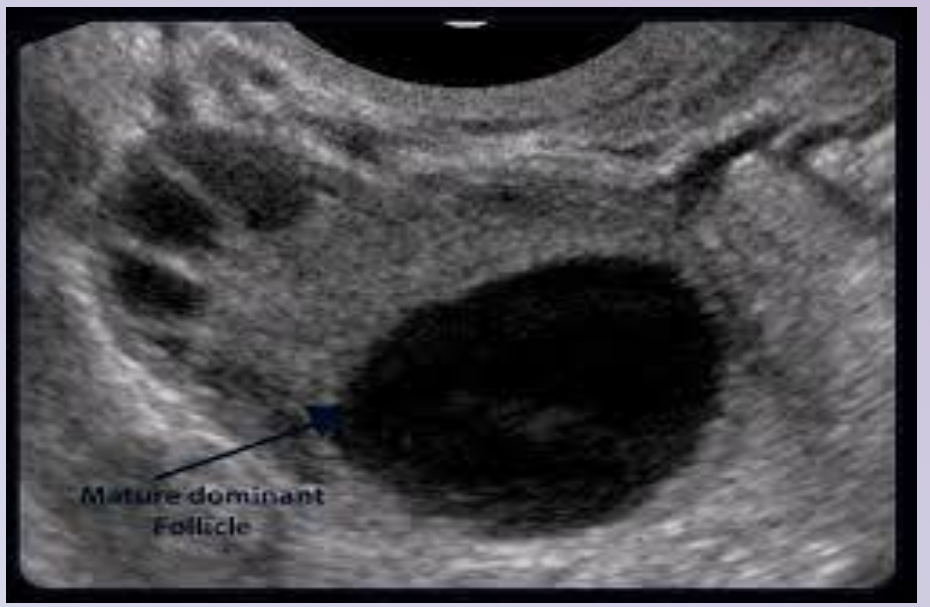
- The basal body temperature (BBT) chart is a simple means of determining whether ovulation has occurred.
- The woman's temperature is taken daily with a thermometer on awakening, before any activity, and is recorded on a graph.
- After ovulation, rising progesterone levels increase the basal temperature by approximately 0.4Â°F (0.22Â°C) through a hypothalamic thermogenic effect.
-

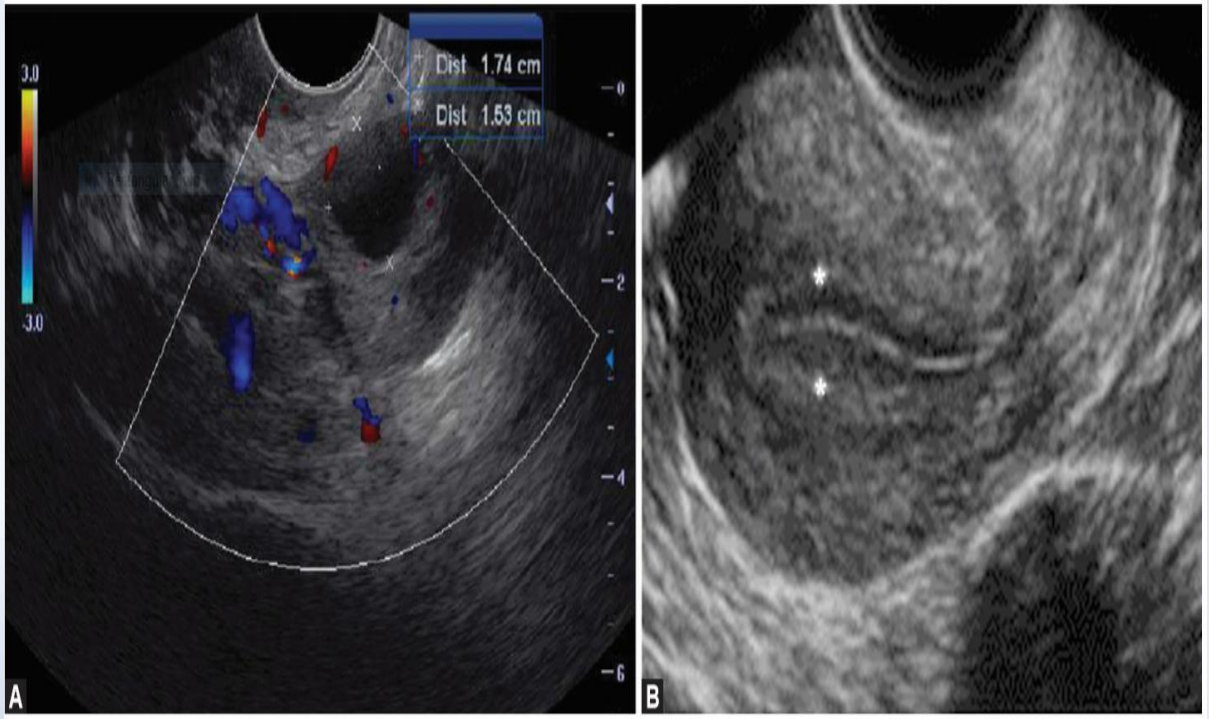
➢ *The period of highest fertility spans 7 days prior to midcycle rise in BBT*

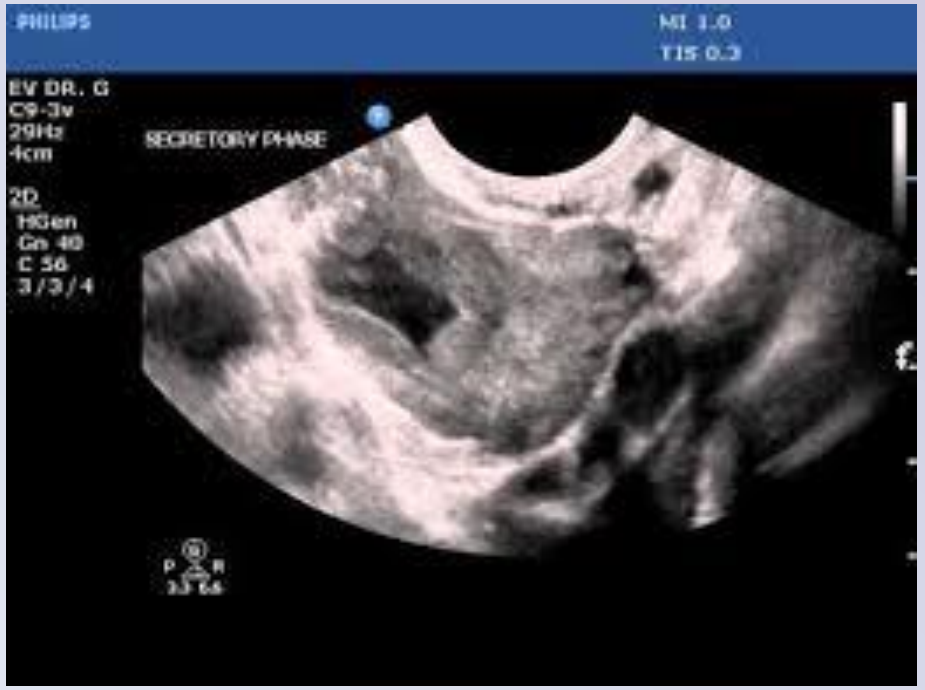
- Ovulatory cycles have clear ***biphasic rise*** in BBT recording and anovulatory cycles have monophasic patterns
- the test cannot reliably define the time of ovulation and can be tedious and increase anxiety

Transvaginal sonography is done to:

- Reveal size and number of developing follicle
- Progressive follicular growth
- Sudden collapse of follicle
- Loss of clear margins
- Appearance of internal echoes
- Increase in cul-de-sac fluid volume







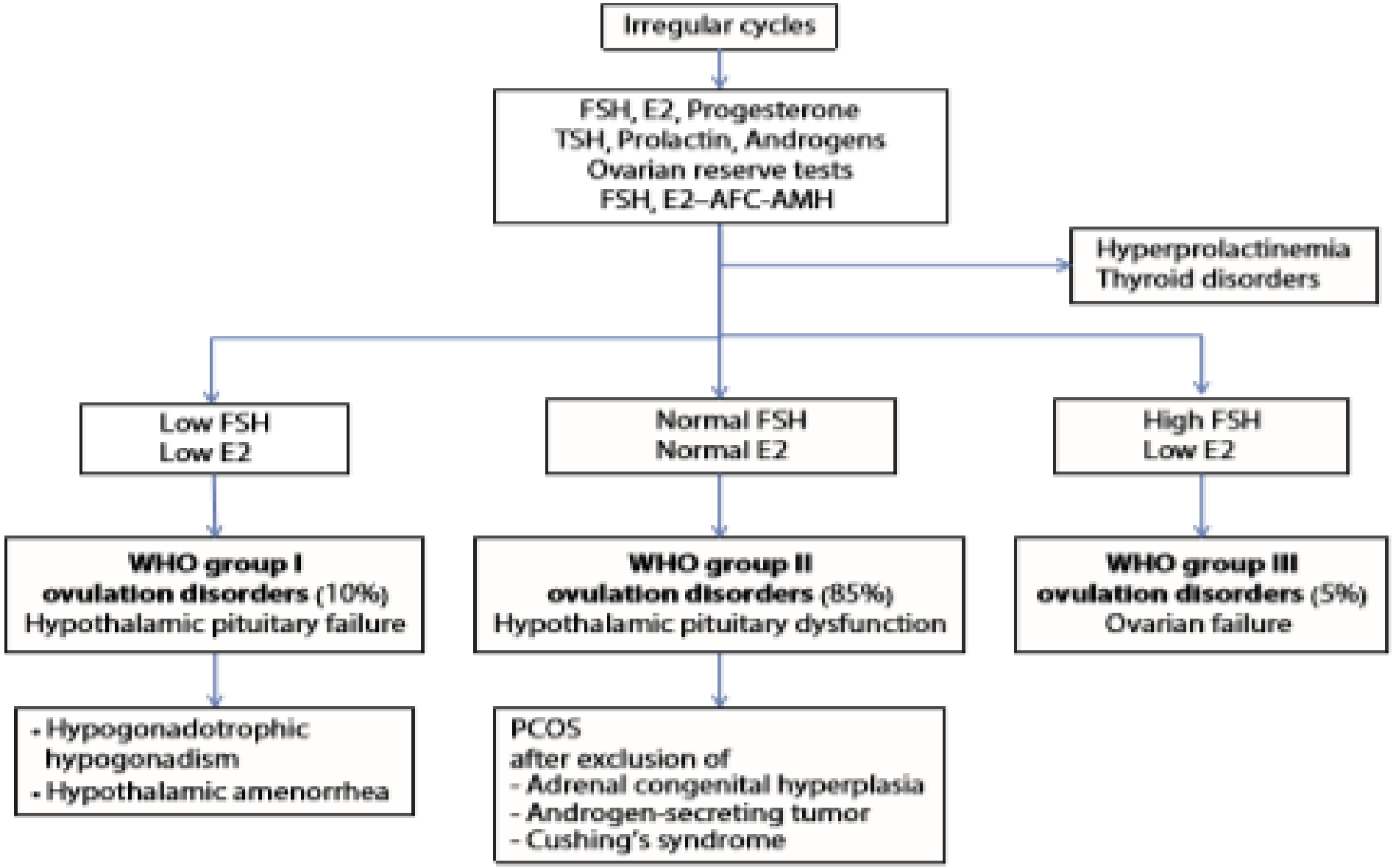
Histological Endometrial Dating

- *Histological endometrial dating* is not a valid diagnostic method because it lacks both accuracy and precision

- It should be done only in those females with suspected specific endometrial pathology (e.g. hyperplasia, neoplasia and endometritis)

- Other evaluations aimed at defining the best choice of treatment may be indicated for anovulatory infertile women.
- **Serum thyroid-stimulating hormone** (TSH) and **prolactin** determinations can identify thyroid disorders and/or hyperprolactinemia, which may require specific treatment.

- In women with amenorrhea, **serum follicle-stimulating hormone** (FSH) and **estradiol** measurements can distinguish women with
  - **Ovarian failure** (**high FSH,low estradiol**) ,whom may be candidates for oocyte donation, from those with
  - **Hypothalamic amenorrhea** (**low or normal FSH,low estradiol**), who will require exogenous gonadotropin stimulation for ovulation induction.


Irregular cycles
FSH, E2, Progesterone
TSH, Prolactin, Androgens
Ovarian reserve tests
FSH, E2–AFC-AMH
Hyperprolactinemia
Thyroid disorders
Low FSH
Low E2
Normal FSH
Normal E2
High FSH
Low E2
WHO group I
ovulation disorders (10%)
Hypothalamic pituitary failure
WHO group II
ovulation disorders (85%)
Hypothalamic pituitary dysfunction
WHO group III
ovulation disorders (5%)
Ovarian failure
- Hypogonadotrophic hypogonadism
- Hypothalamic amenorrhea
PCOS
after exclusion of
- Adrenal congenital hyperplasia
- Androgen-secreting tumor
- Cushing's syndrome

- In anovulatory infertile women, failure to achieve pregnancy after three to six cycles of successful ovulation induction should be viewed as an indication to perform additional diagnostic evaluation or, if evaluation is complete, to consider alternative treatments.

- Women with sign and symptoms of hyperandrogenism require further investigations:

Serum Te

ð 4androstenedione

DHEA-S

17Hydroxy progestrone

2- Assessment of Ovarian Reserve

- The concept of‘‘ ovarian reserve’’ views reproductive potentialas a function of the number and quality of remaining oocytes.
- Decreased or diminished ovarian reserve (DOR) describes women of reproductive age having regular menses whose response to ovarian stimulation is reduced compared to those women of comparable age.

- Tests utilized to assess ‘‘ ovarian reserve ’’ Include :
  - **cycle day 3 FSH and estradiol measurements,**
  - **a clomiphene citrate challenge test**
  - **an early follicular phase antral follicle count (via transvaginal ultrasonography), or**
  - **a serum antimuullerian hormone (AMH) level**

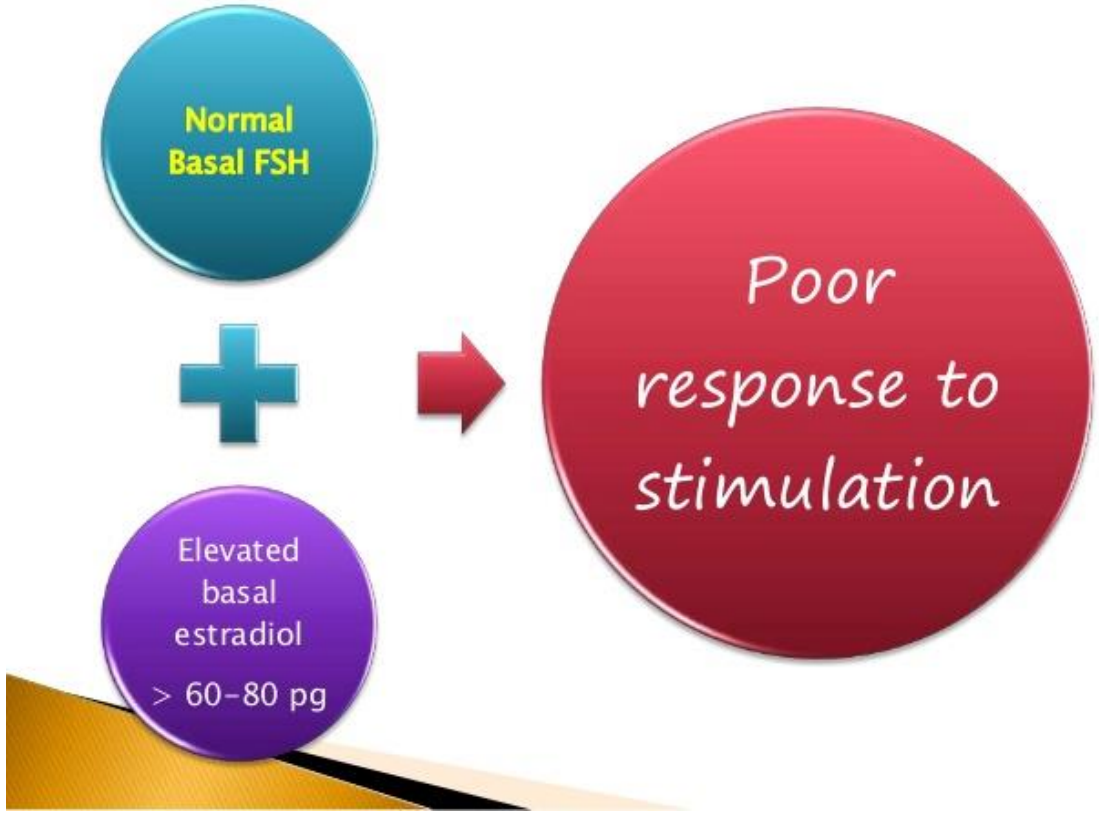
- These tests may provide prognostic information in women at increased risk of diminished ovarian reserve, such as women who:
- 1) are over age 35 years;
- 2) have a family history of early menopause;
- 3) have a single ovary or history of previous ovarian surgery, chemotherapy, or pelvic radiation therapy;
- 4) have unexplained infertility
- 5) have demonstrated poor response to gonadotropin stimulation; or
- 6) are planning treatment with assisted reproductive technology(ART)

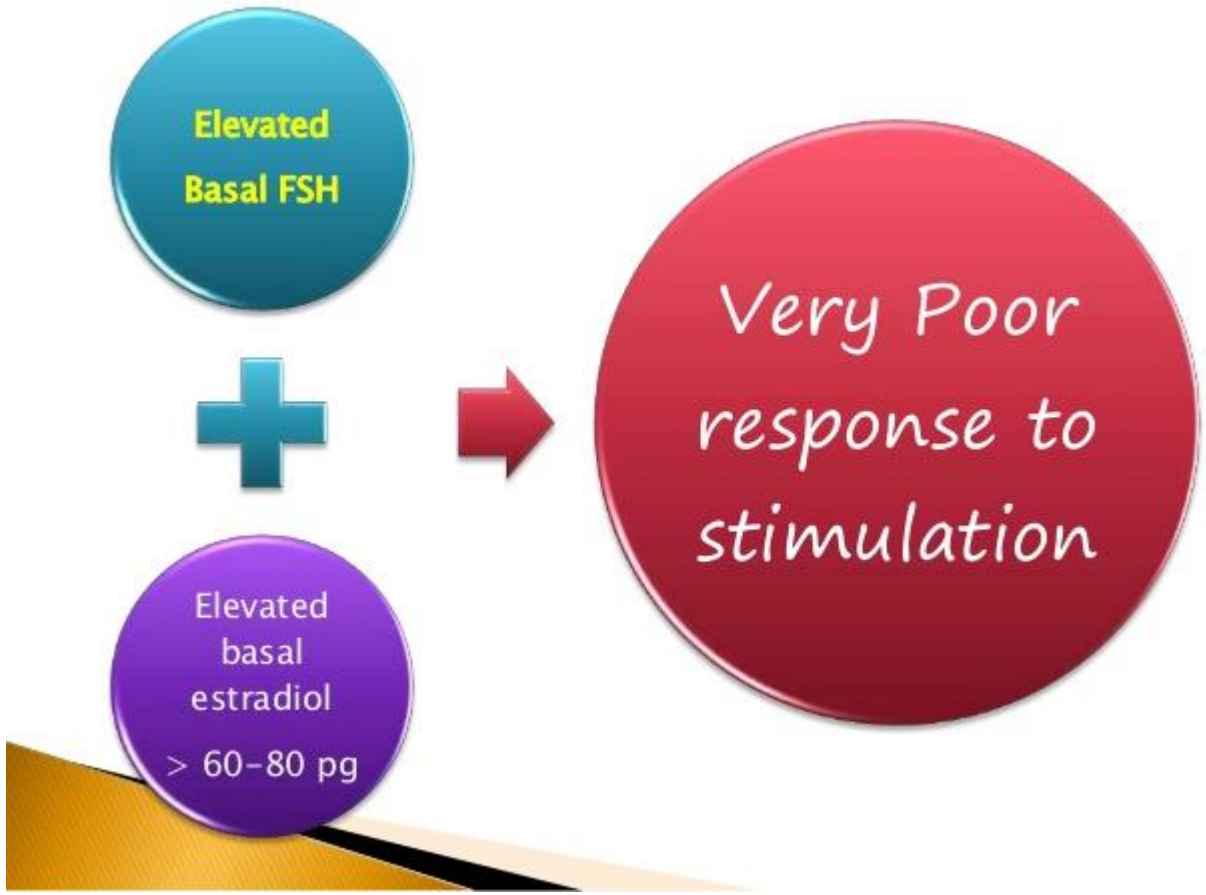
Cycle Day 3 FSH and Estradiol

- FSH obtained on cycle day 2–5 is commonly used as a measure of ovarian reserve.
- High values (10–20 IU/L) have been associated with both poor ovarian stimulation and the failure to conceive.
-

Cycle D3 FSH and E2

- Obtained on D2-5 FSH 10-20 IU/L is high
- Estradiol is used only to correctly interpret the FSH basal serum level
- If FSH is normal and E2 is more than 60 to 80 pg/mL, there is limited evidence for association with poor response, increased cancelation rate and low pregnancy
- If several values are obtained in the same patient , the highest value is considered to be prognostic
- The upper threshold of FSH varies between 8/9 and 25IU/L


Normal
Basal FSH
Elevated
basal
estradiol
> 60-80 pg
Poor
response to
stimulation

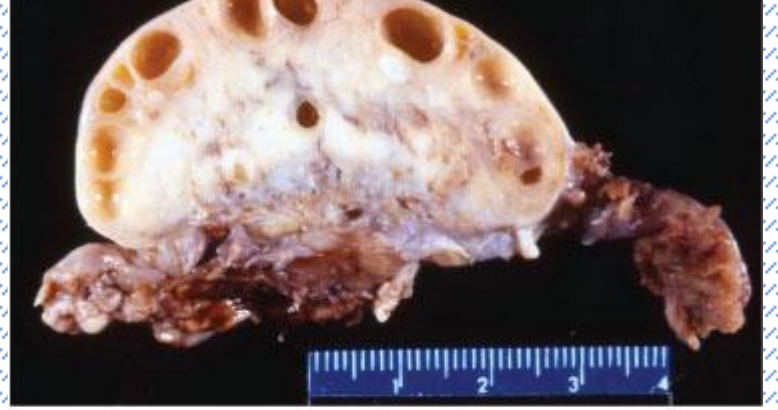

Elevated
Basal FSH
Elevated
basal
estradiol
> 60-80 pg
Very Poor
response to
stimulation

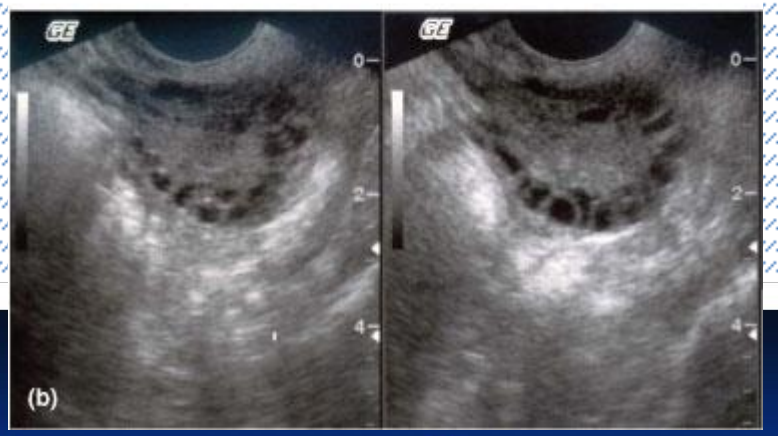
Clomiphene Citrate Challenge Test

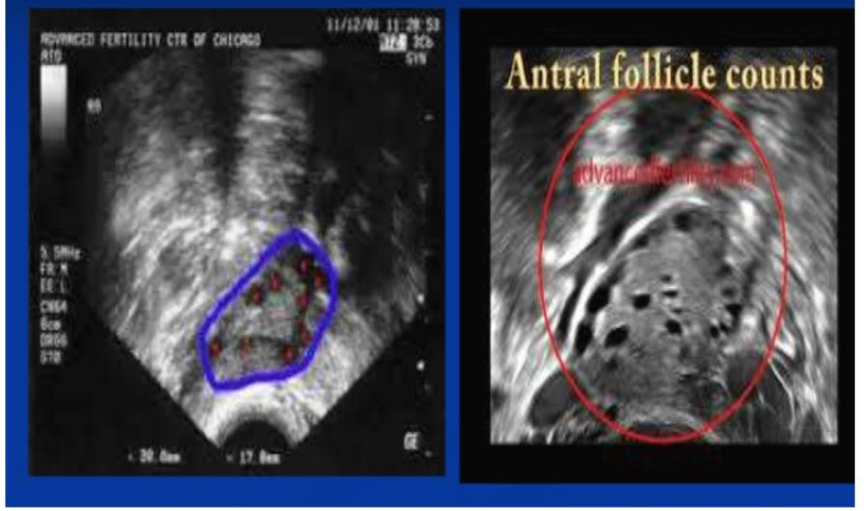
- The CCCT involves measurements of serum FSH before and after treatment with clomiphene citrate (100 mg daily, cycle days 5–9), typically on cycle day 3 and cycle day 10.
- An elevated FSH concentration after clomiphene stimulation therefore suggests DOR.
- Cycle day 10 FSH levels have a higher sensitivity but lower specificity compared to cycle day 3 FSH concentrations

Antral follicle count (AFC)

- Ultrasound examination can be used to determine the number of antral follicles (defined as follicles measuring 2 to 10 mm in diameter). On transvaginal ultrasound,
- The ovaries are visualized in their transverse and longitudinal planes and the antral follicles are counted and measured; the size of the follicle is the mean of two perpendicular diameters, one of which should be the largest dimension of each follicle



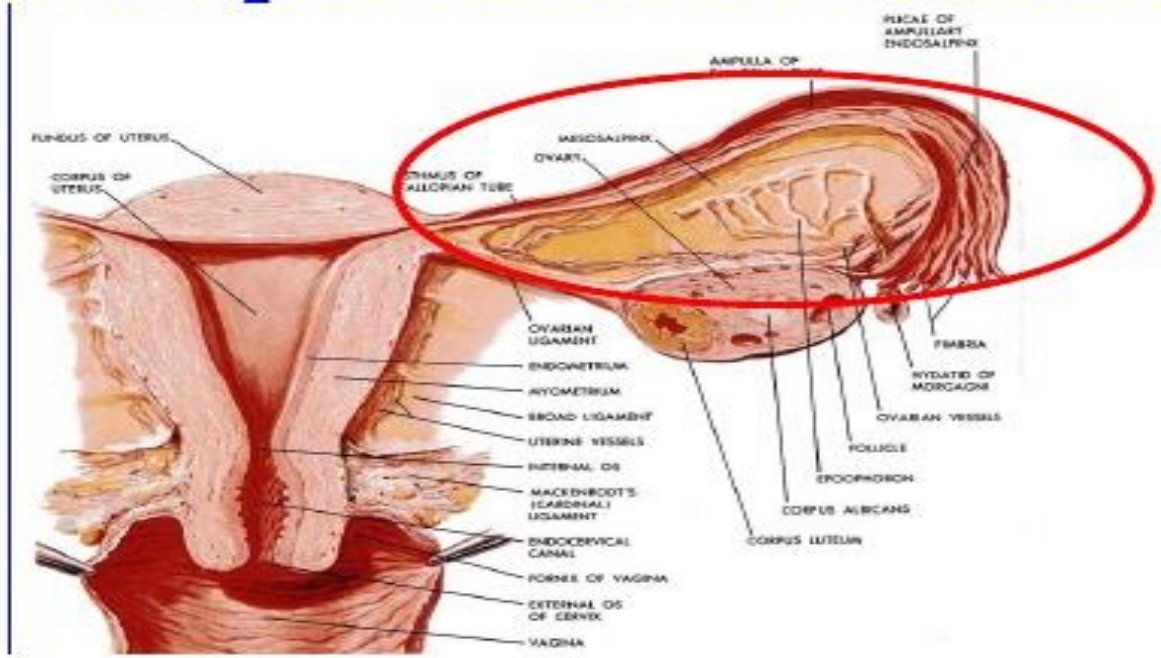




Serum Antimullerian Hormone (AMH) Level

- Serum concentrations of AMH, produced bygranulosa cells of early follicles, are gonadotropin-independent and therefore remain relatively consistent within and between menstrual cycles in both normal young ovulating women and in women with infertility
- Therefore an AMH level can be obtained on any day of the menstrual cycle.
- Overall, lowerAMH levels (<1 ng/mL) have been associated with poor responses to ovarian stimulation, poor embryo quality, and poor pregnancy outcomes in IVF

Tubal/peritoneal factor

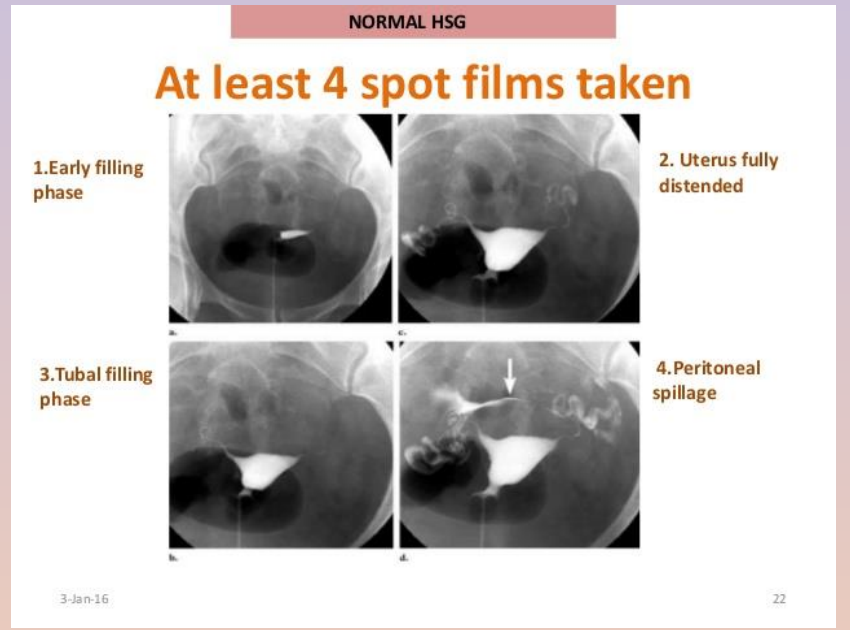


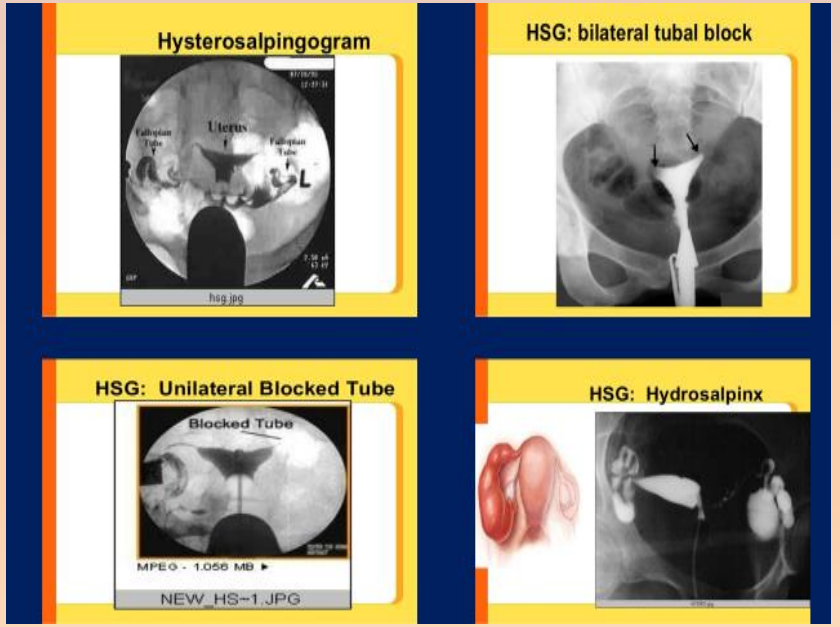
- Anatomical changes (congenital malformations, BTL, adhesions, endometriosis)

FALLOPIAN TUBE ABNORMALITIES/PELVIC ADHESIONS

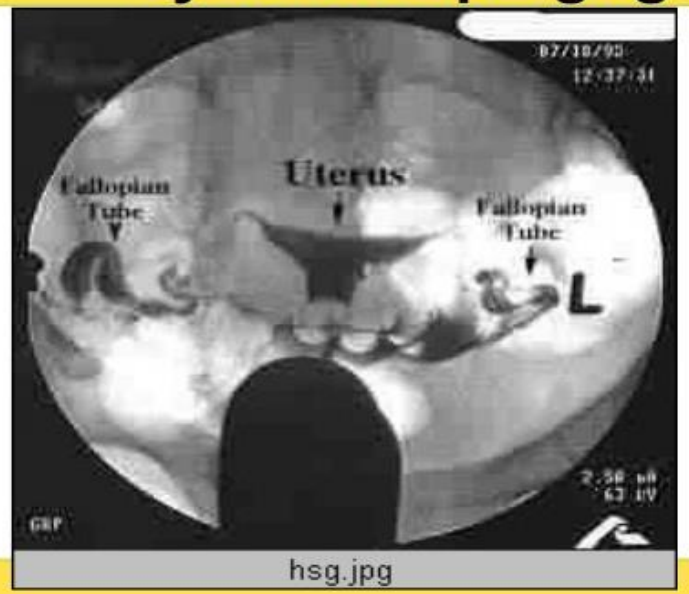
- Tubal disease and pelvic adhesions prevent normal transport of the oocyte and sperm through the fallopian tube
- The primary cause of tubal factor infertility is pelvic inflammatory disease caused by pathogens such as chlamydial or gonorrhea
- Other conditions that may interfere with tubal transport include
  - severe endometriosis
  - adhesions from previous surgery or non-tubal infection (eg, appendicitis, inflammatory bowel disease)
  - pelvic tuberculosis
  - salpingitis isthmica nodosa (ie, diverticulosis of the fallopian tube)
- Proximal tubal blockage may result from plugs of mucus and amorphous debris or spasm of the uterotubal ostium, but does not reflect true anatomic occlusion

- **Hysterosalpingography (HSG),** using either a water- or lipid-soluble contrast media, is the traditional and standard method for evaluating tubal patency and may offer some therapeutic benefit.
- HSG can document proximal and distal tubal occlusion, demonstrate salpingitis isthmica nodosa, reveal tubal architectural detail of potential prognostic value, and may suggest the presence of fimbrial phimosis or peritubular adhesions when escape of contrast is delayed or becomes loculated, respectively.

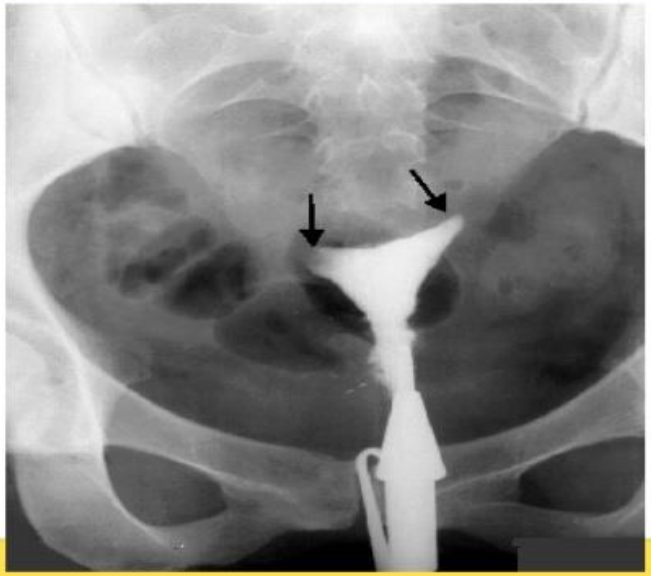




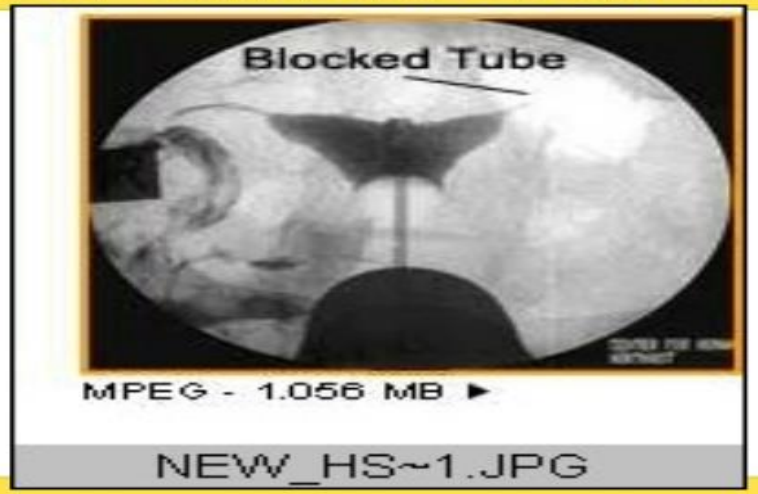
Hysterosalpingogram



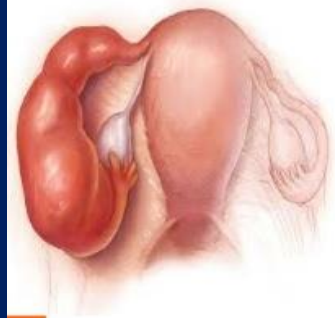
HSG: bilateral tubal block

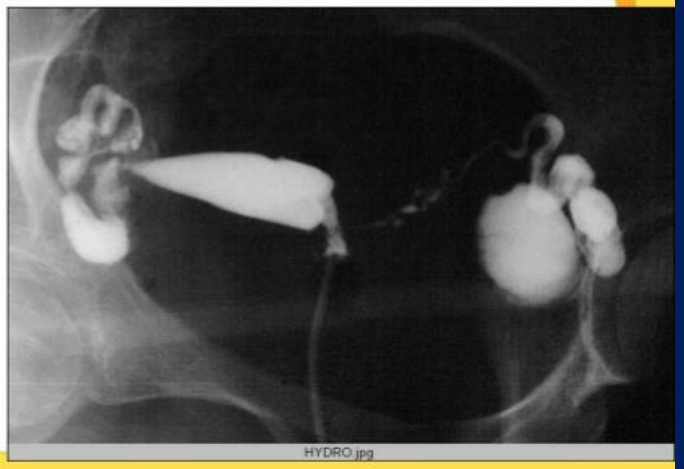


HSG: Unilateral Blocked Tube

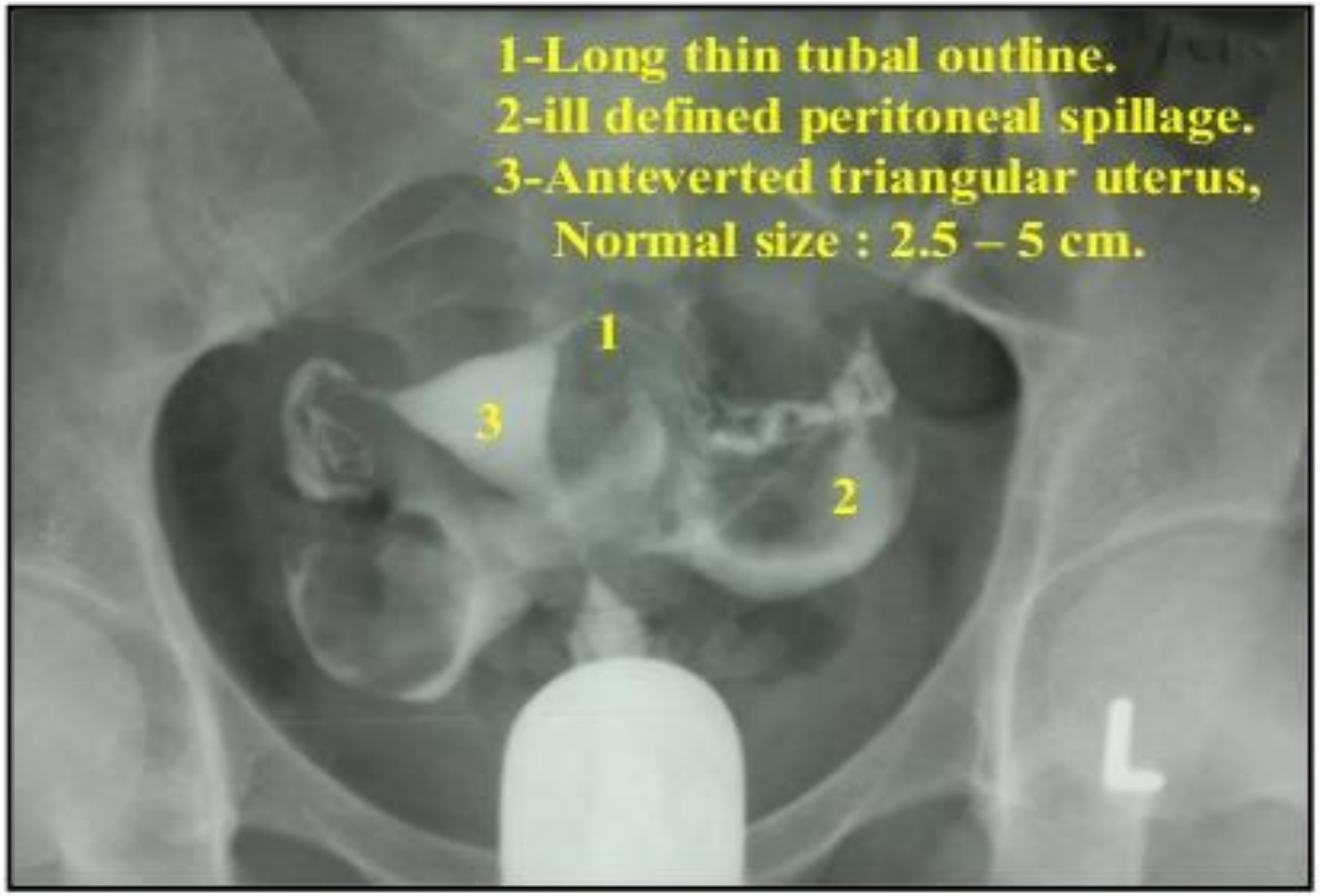


HSG: Hydrosalpinx



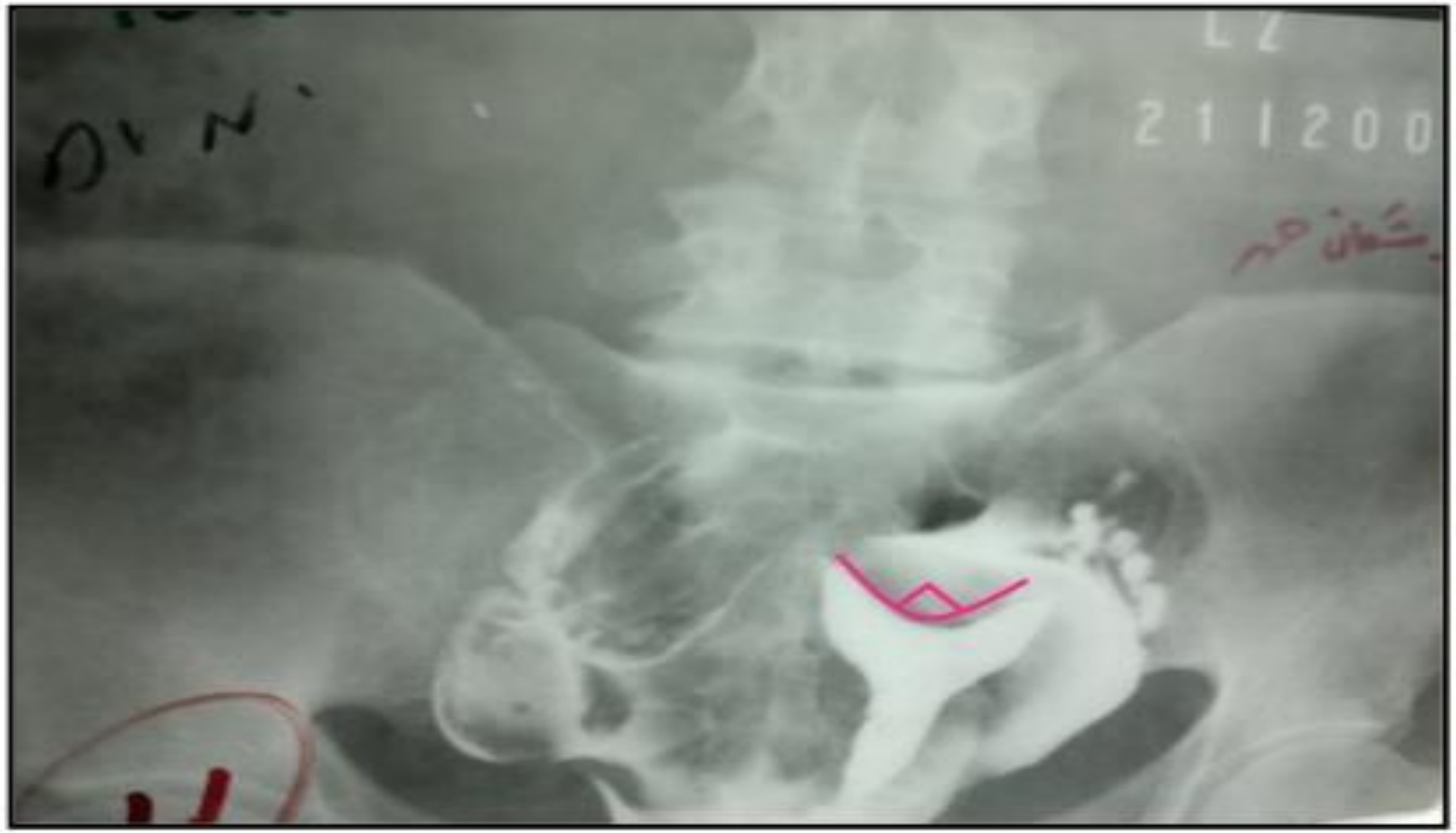


Case 1



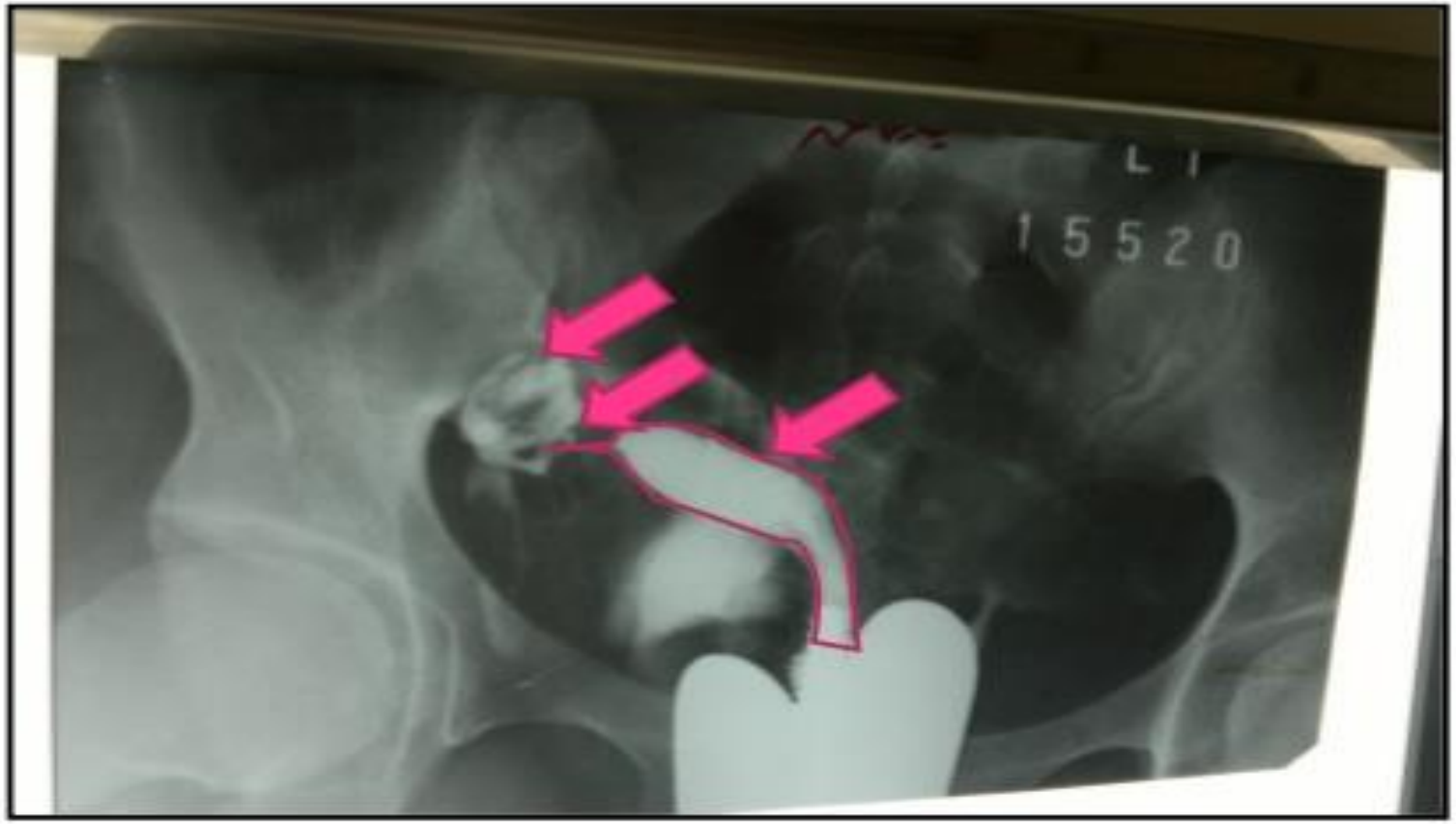
- **Diagnosis:** normal film.
- **Description:** small uterus (nulliparous)

Case 8



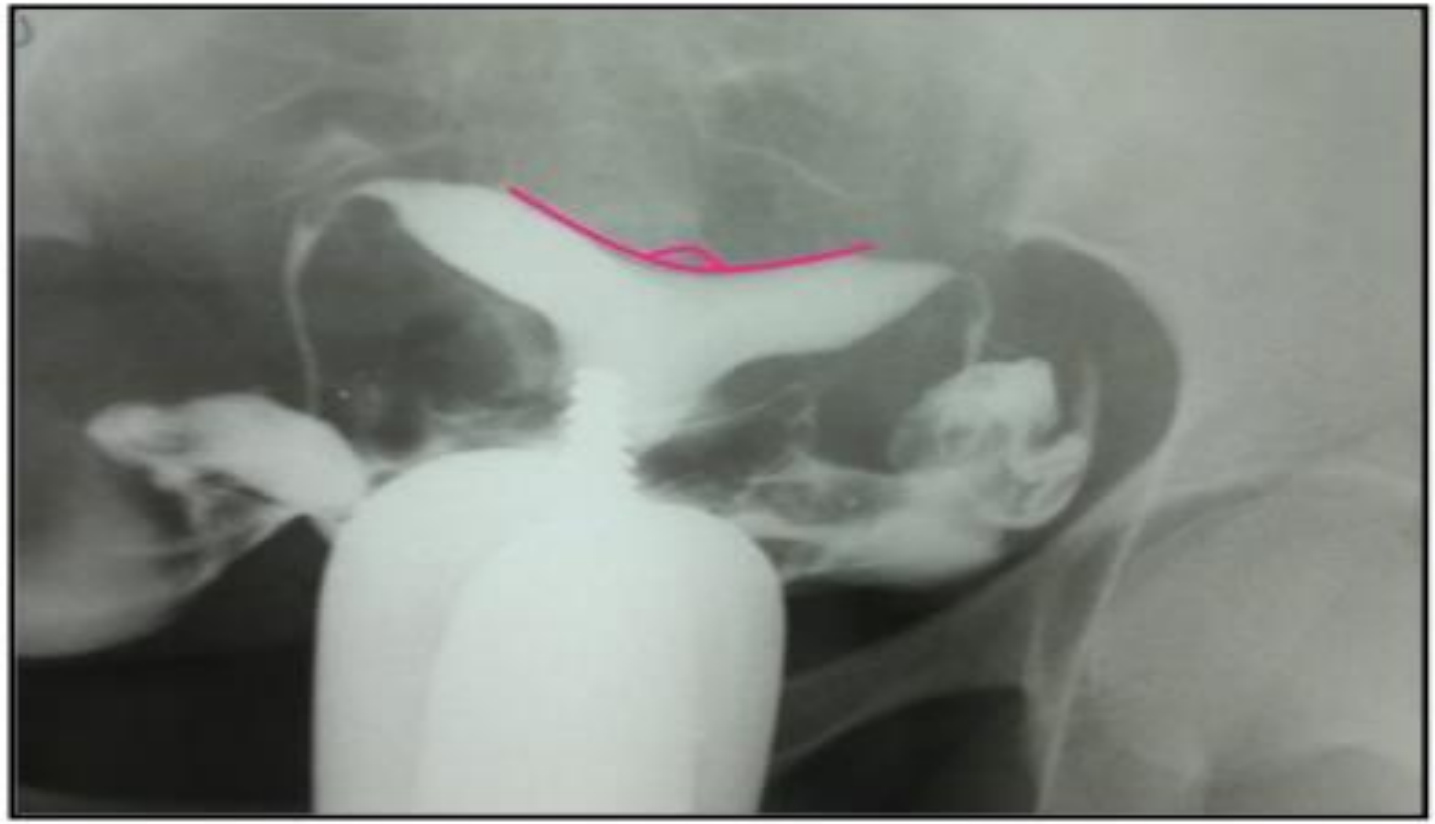
- **Diagnosis:** arcuate uterus.
- **Description:** partial separation (forming right angle).

Case 10



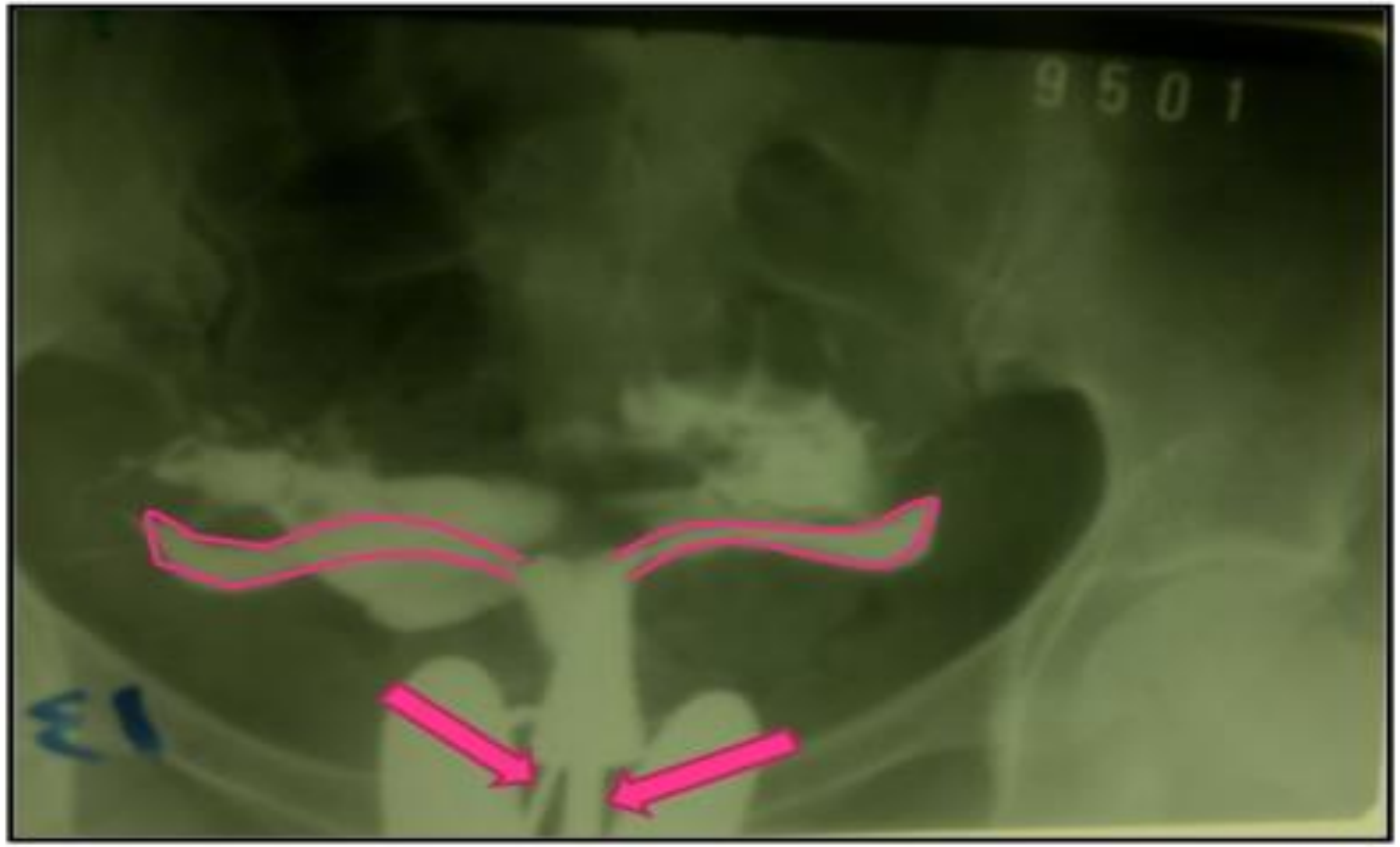
- **Diagnosis:** unicornuate uterus.
- **Description:** one cornua , one tube , one spillage.

Case 13



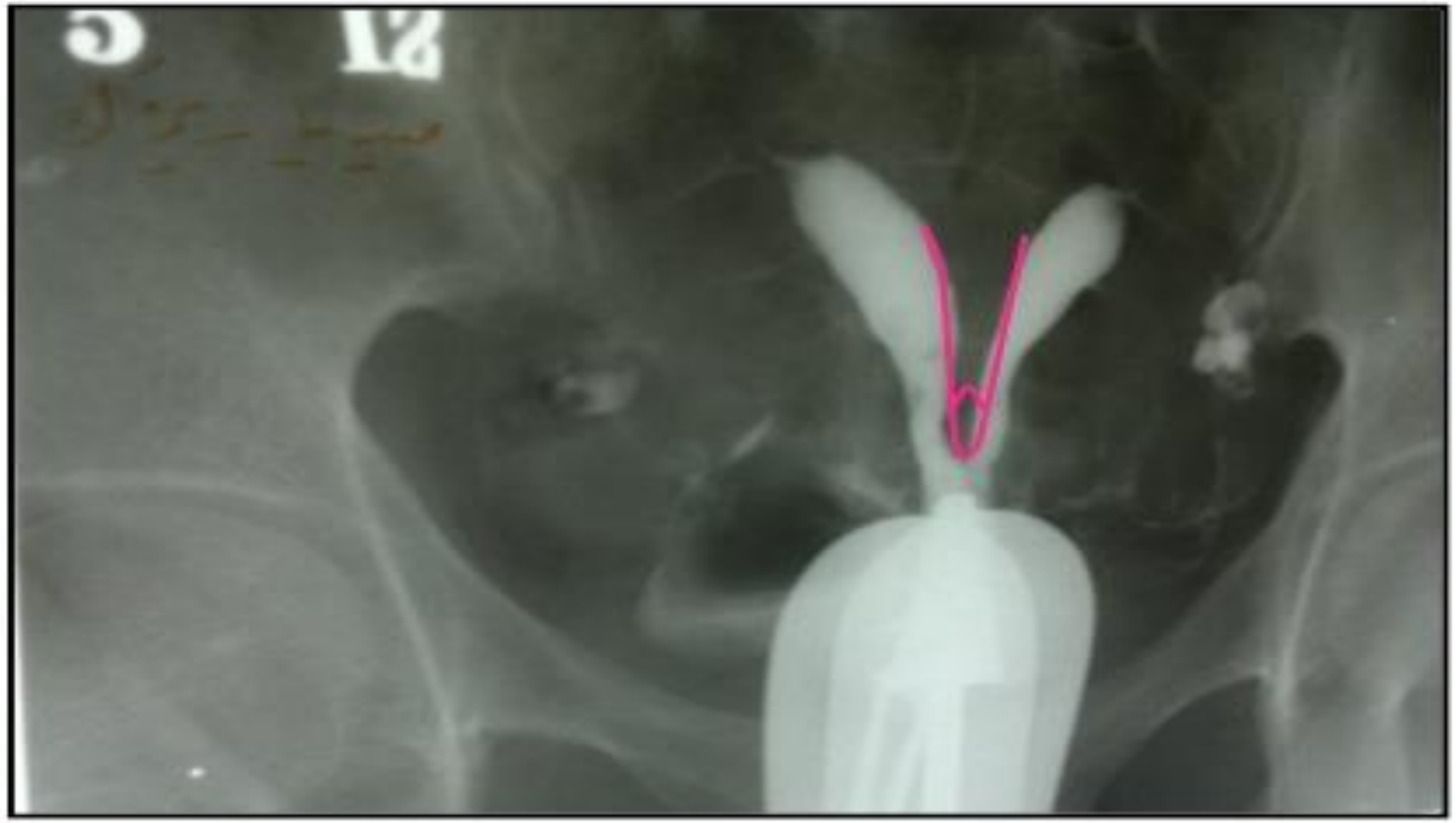
- **Diagnosis:** bicornuate uterus.
- **Description:** complete separation (forming open angle).

Case 16



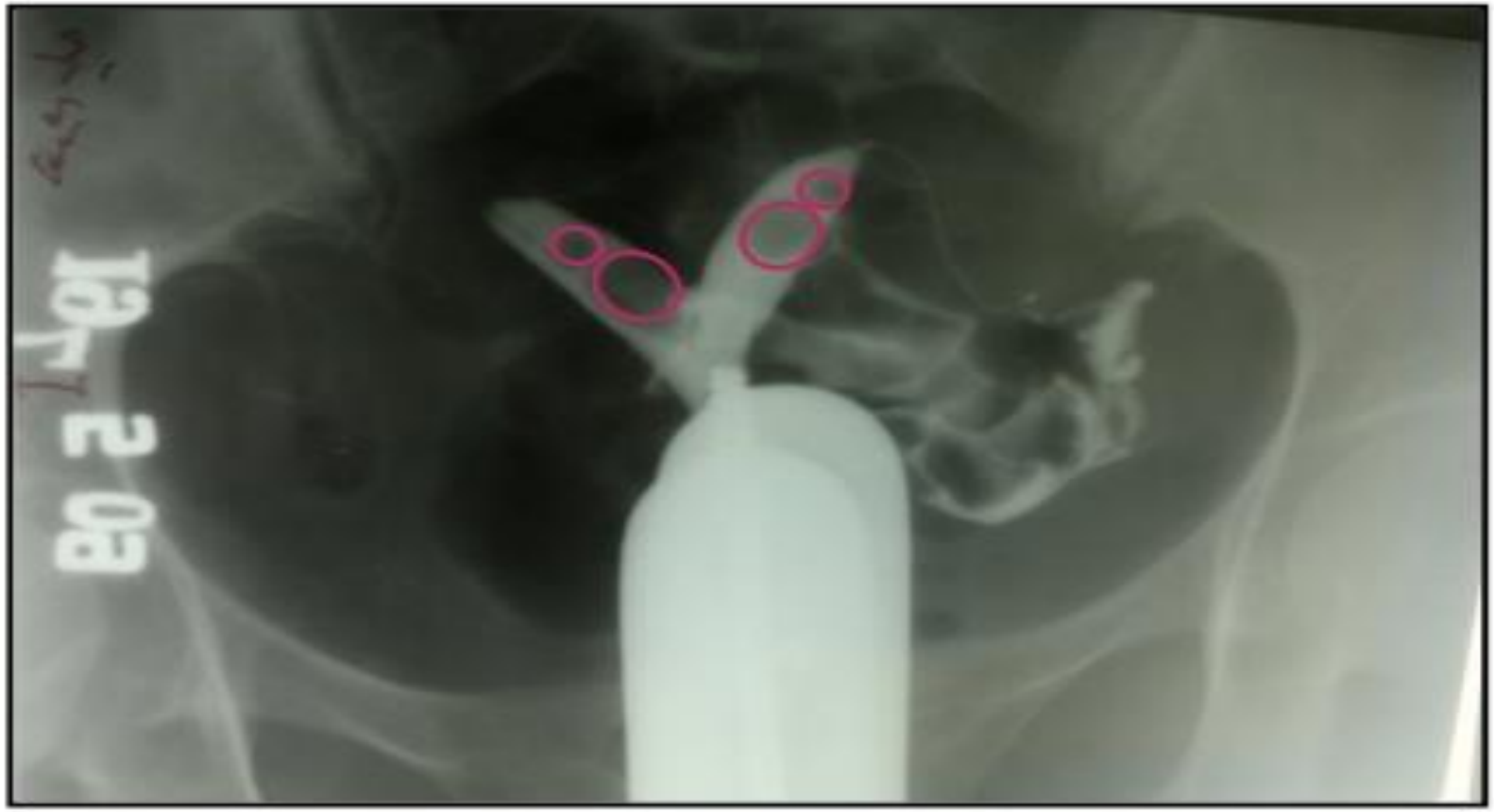
- Diagnosis: complete didelphys uterus.
- Description: two cervix , two uterus (look for two cannula!)

Case 18



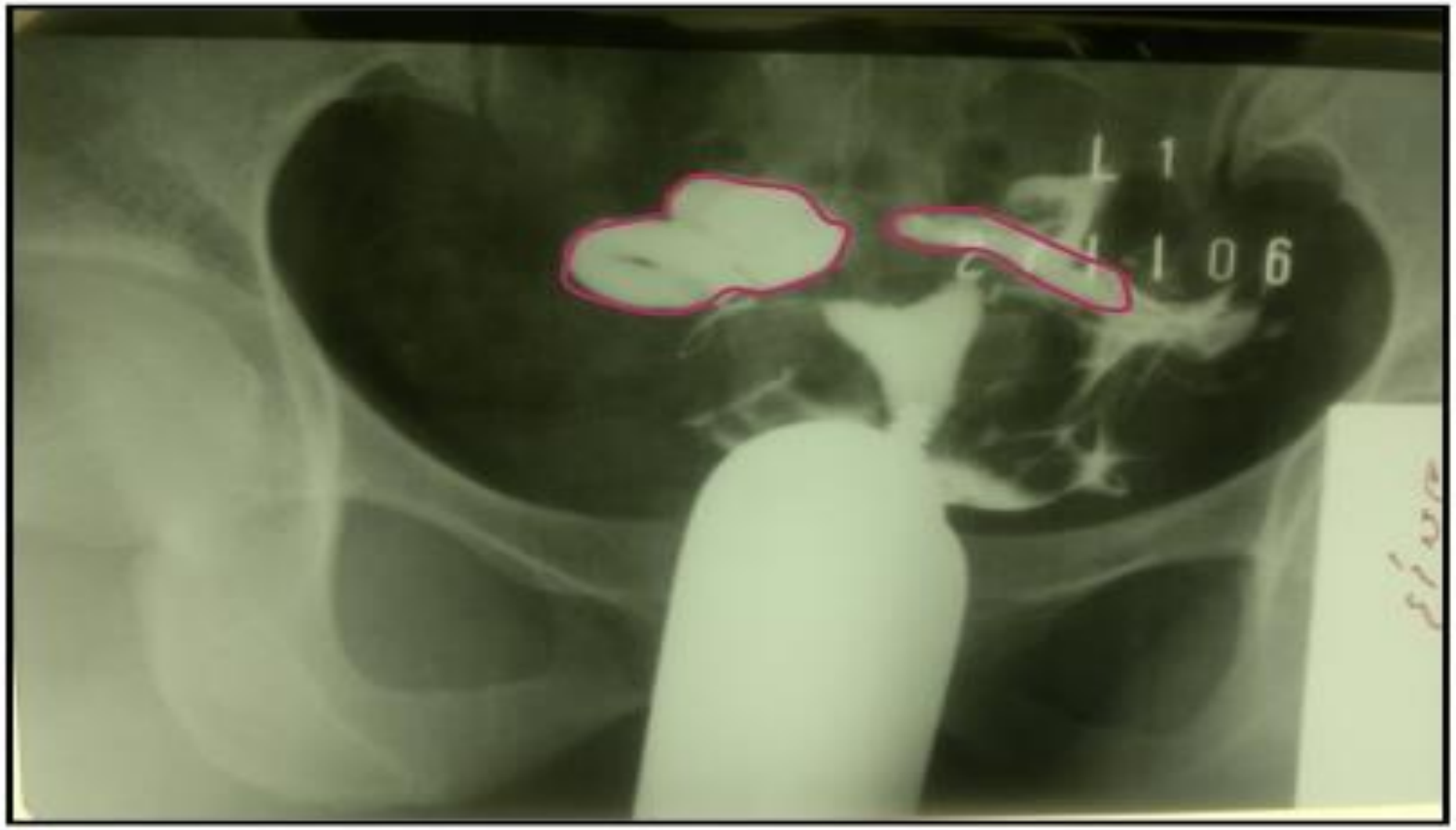
- **Diagnosis:** septate uterus.
- **Description:** slight separation (forming acute angle).

Case 20



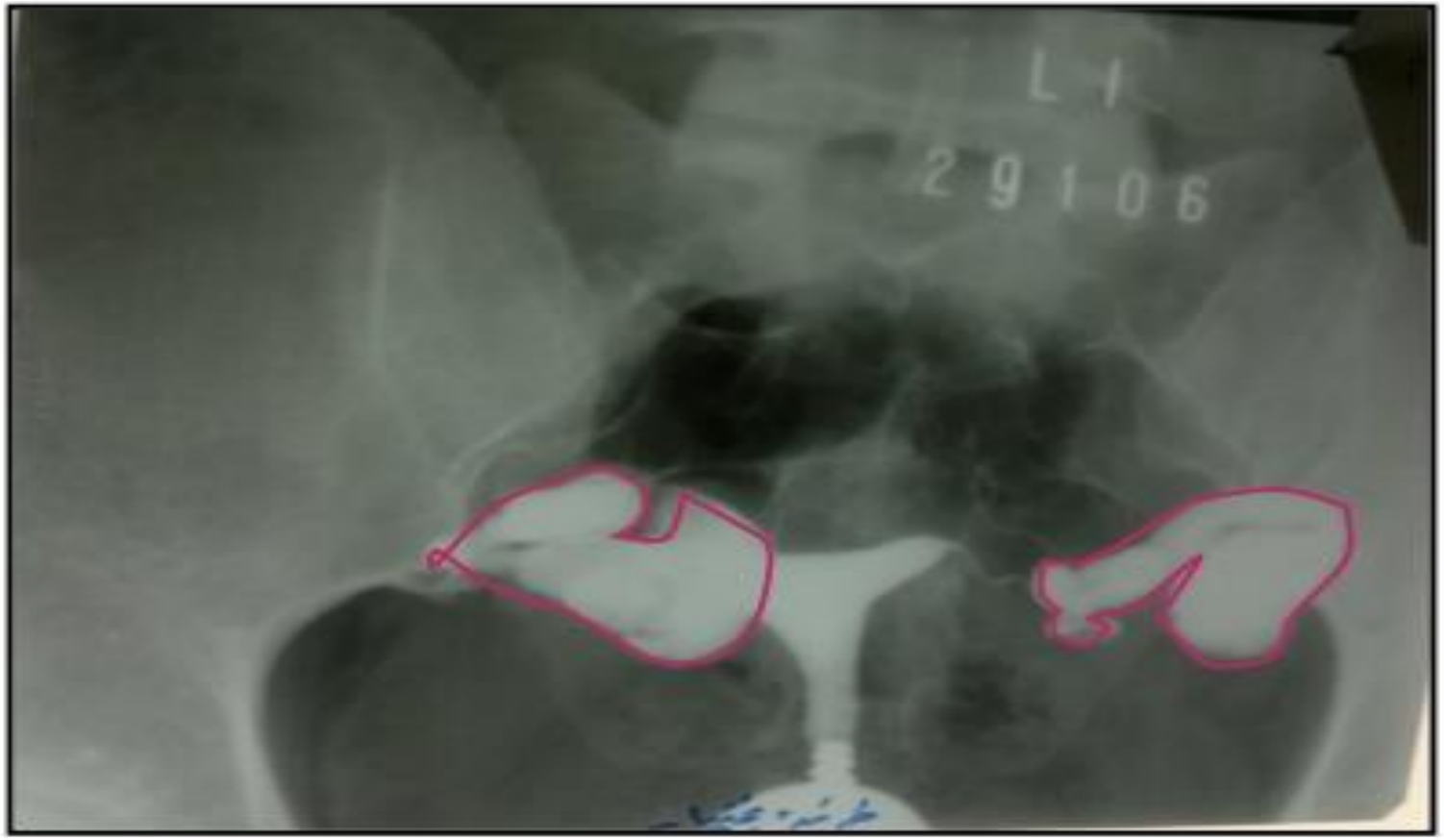
- **Diagnosis:** bicornuate uterus with filling defects.
- **Description:** differential diagnosis: fibroids , air bubbles , bowel gas.

Case 22



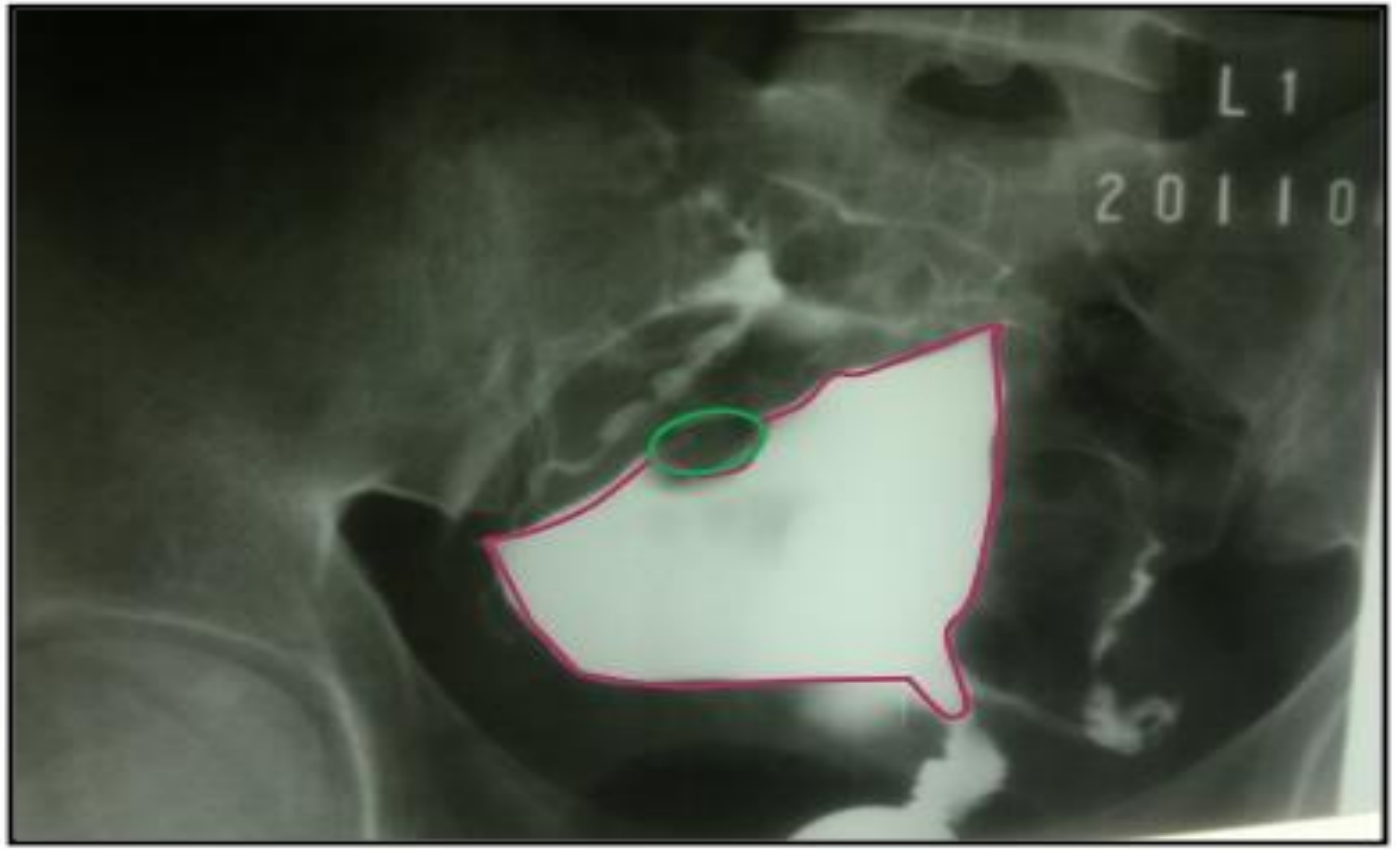
- **Diagnosis:** bilateral hydrosalpinges with patent fallopian tube.
- **Description:** dilatation of tubes.

Case 23



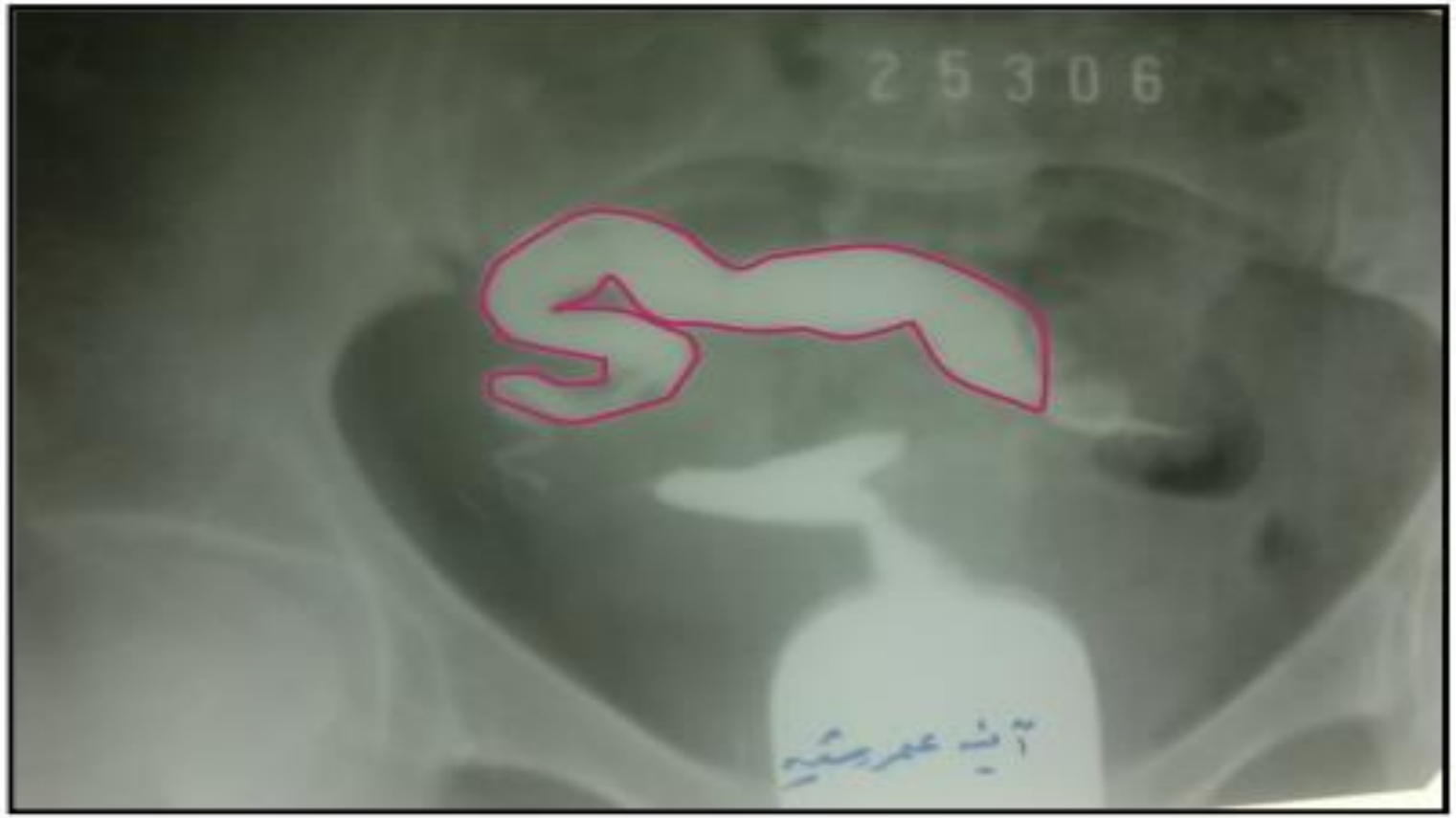
- **Diagnosis:** bilateral hydrosalpinges with patent fallopian tube.
- **Description:** saccular dilatation of tubes.

Case 24



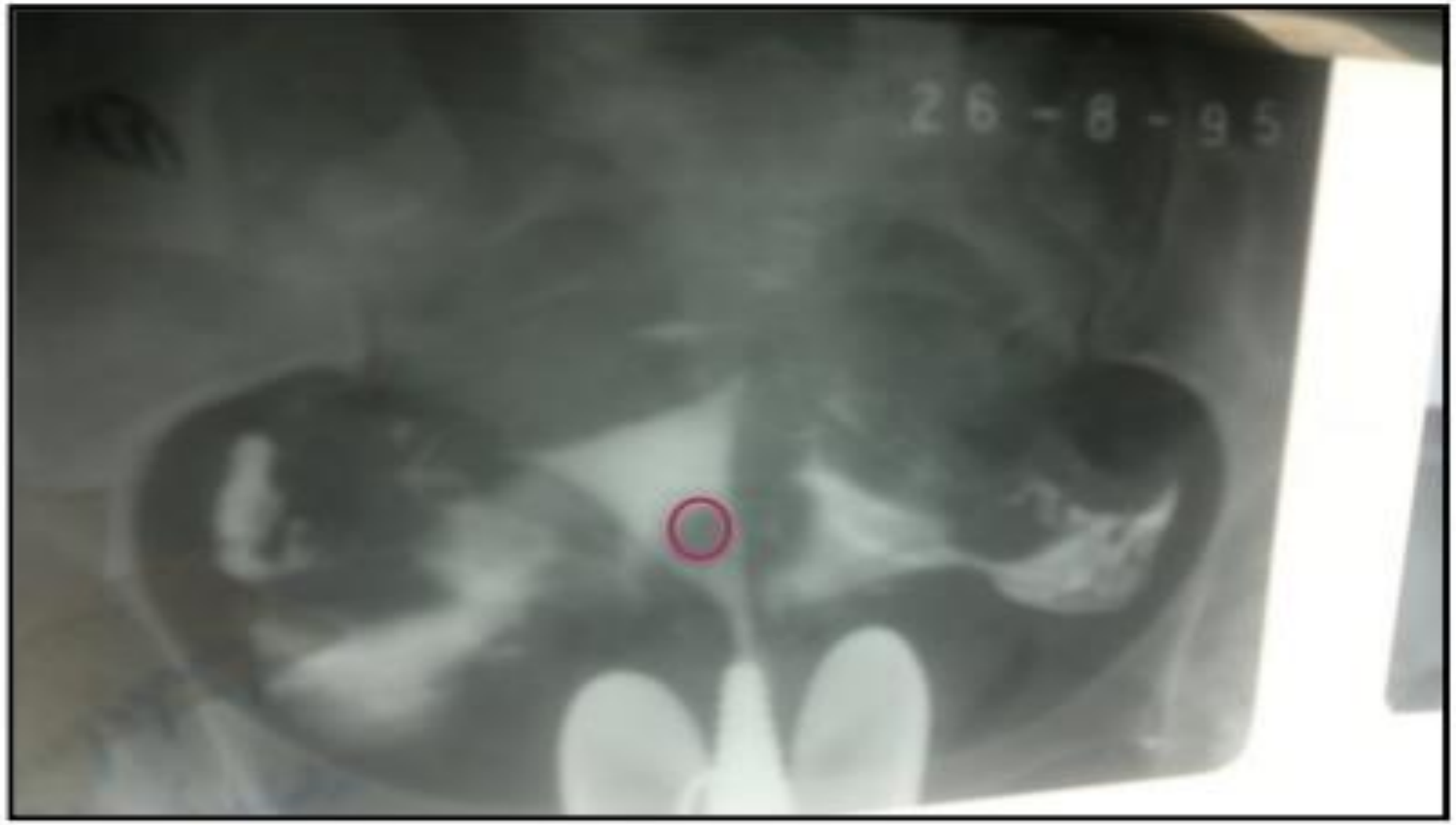
- **Diagnosis:** uterine fibroid.
- **Description:** large, Irregular outline uterus with filling defect.

Case 26



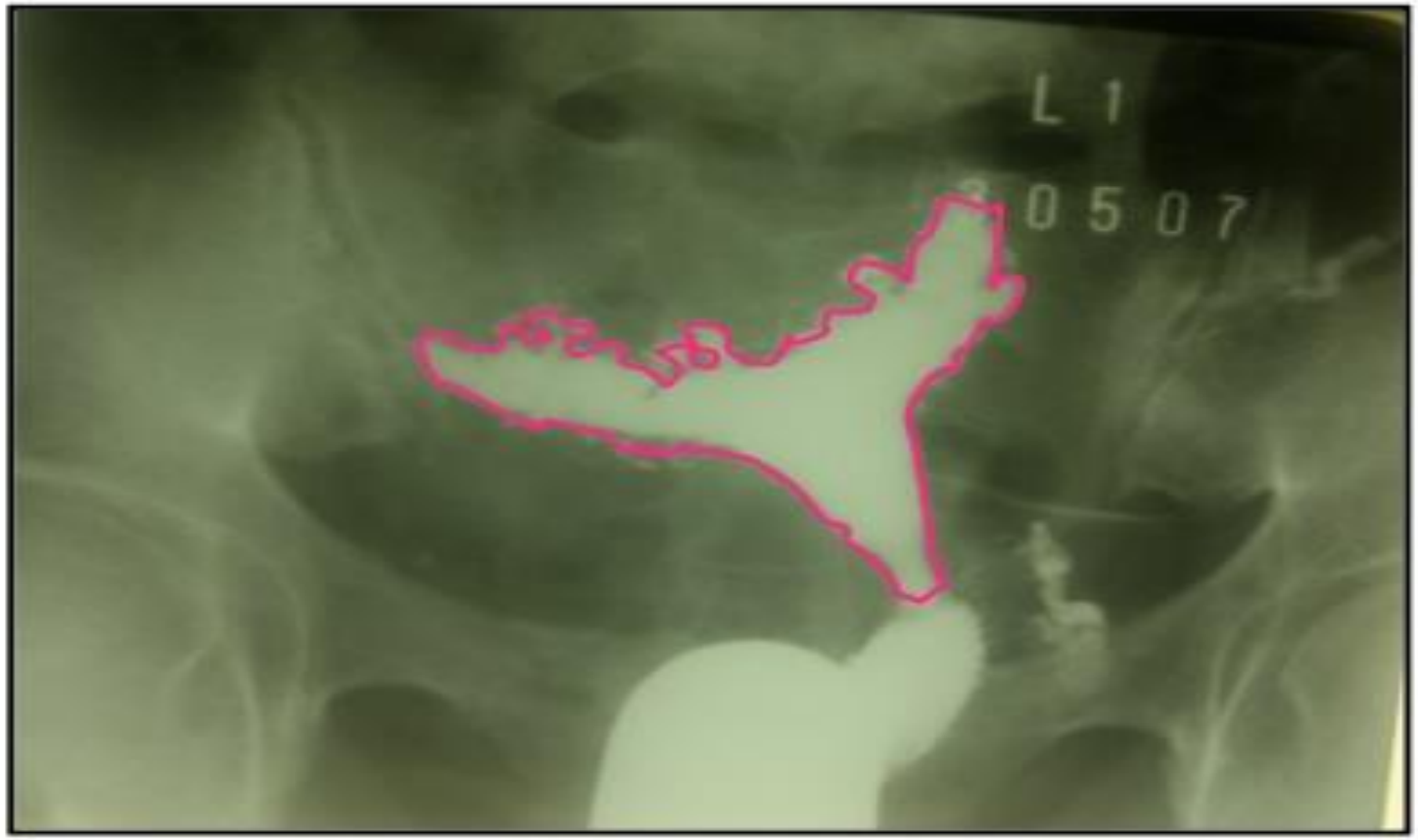
- **Diagnosis:** Hydrosalpinx.
- **Description:** take different size and shape of dilatation (sacculation).

Case 27



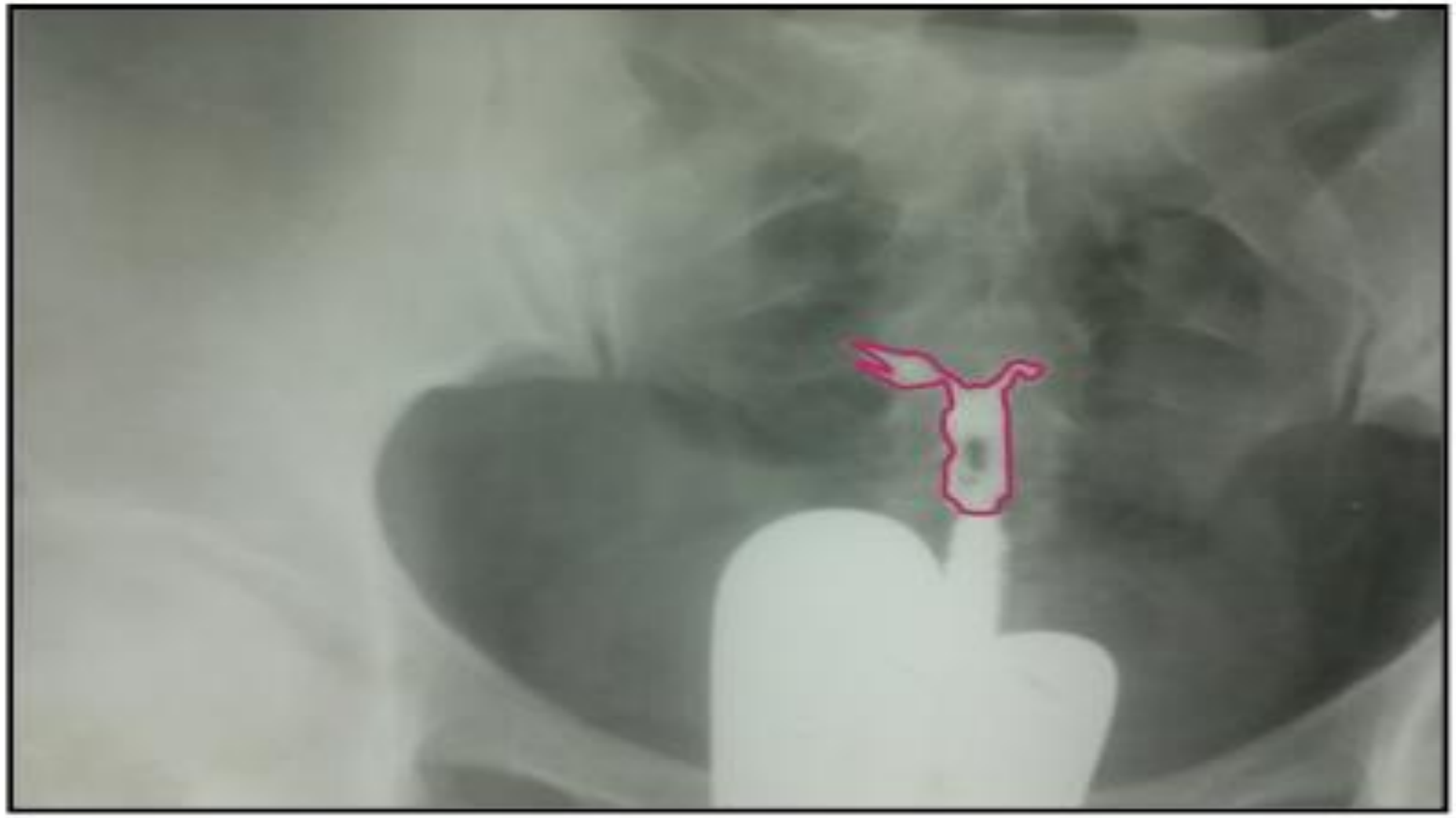
- **Diagnosis:** uterine fibroids.
- **Description:** constant filling defect (immobile).

Case 30



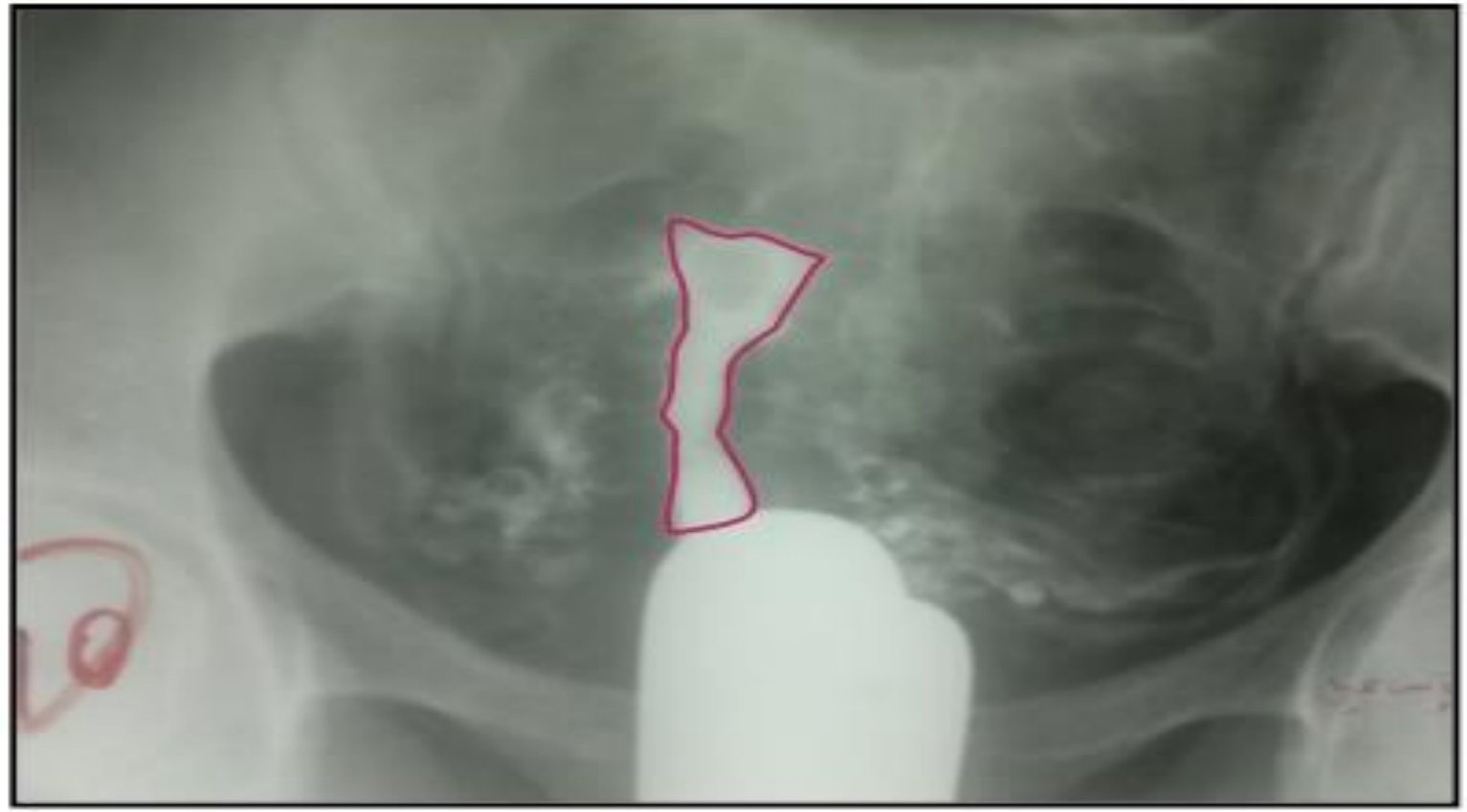
- Diagnosis: adenomyosis.
- Description: irregular outline, multiple diverticulum..

Case 31



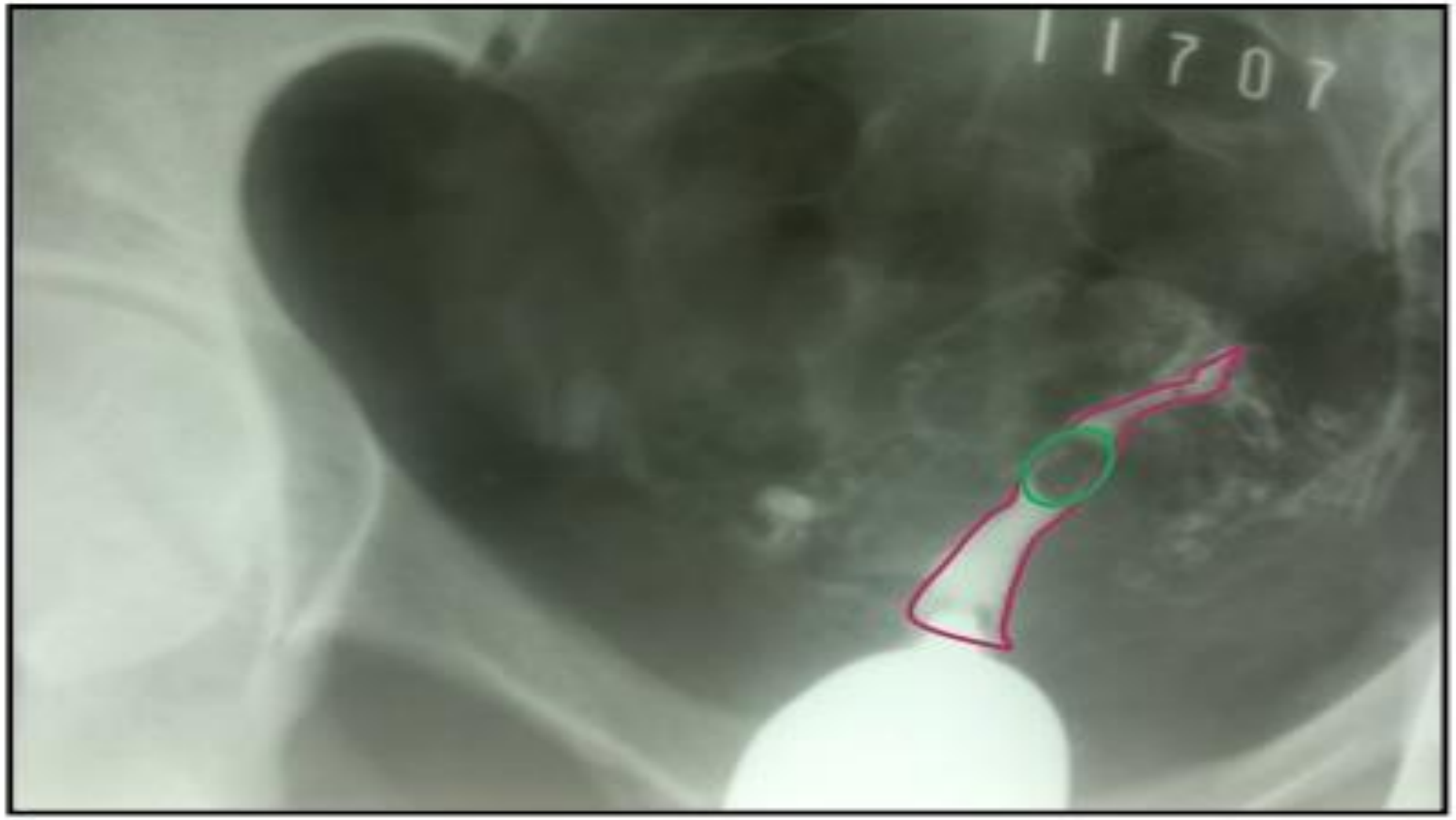
- **Diagnosis:** small narrow uterus.
- **Description:** differential diagnosis : Asherman ,DC, TB uterus.

Case 32



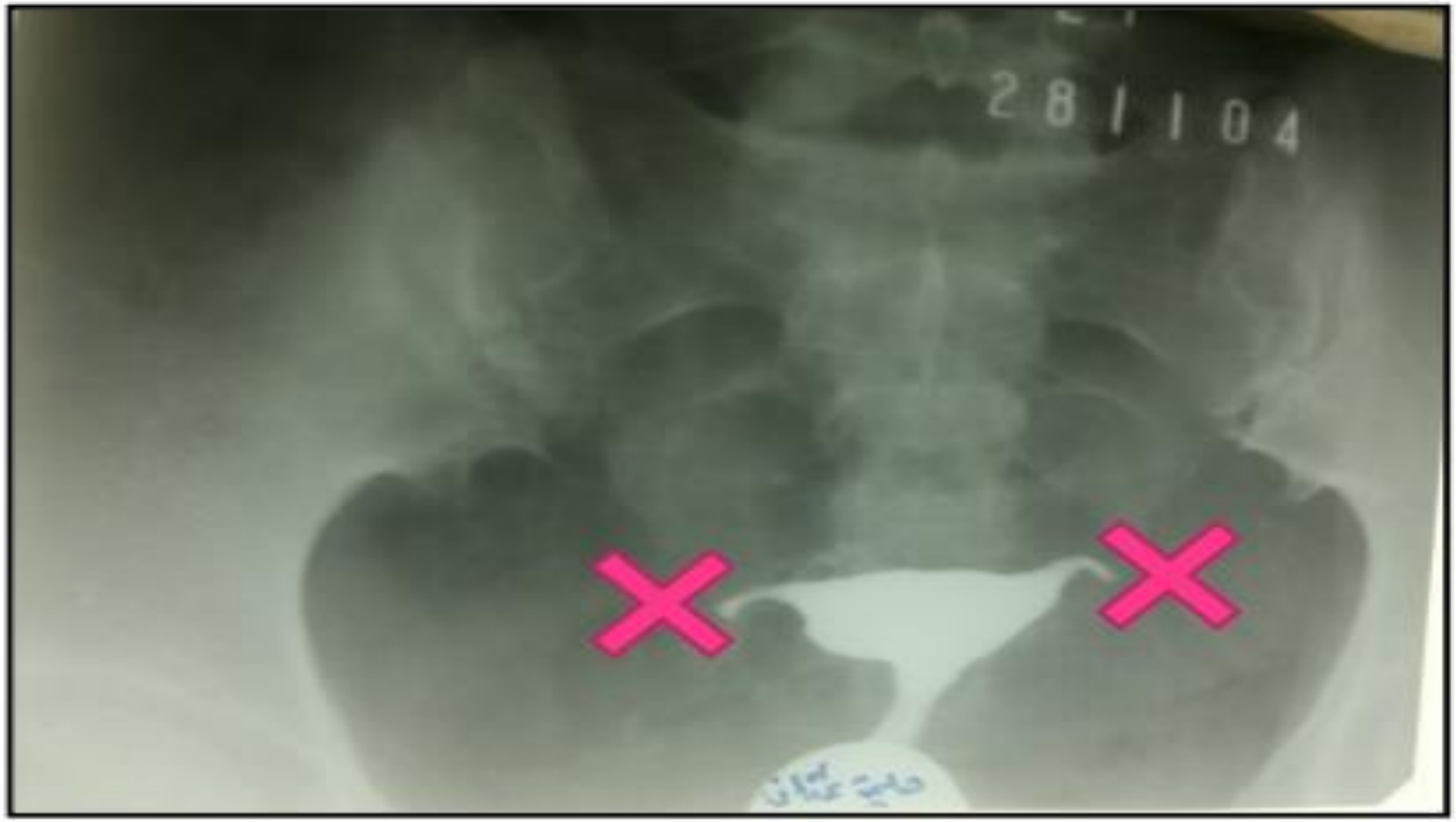
- **Diagnosis:** small narrow uterus.
- **Description:** differential diagnosis : Asherman ,DC, TB uterus.

Case 33



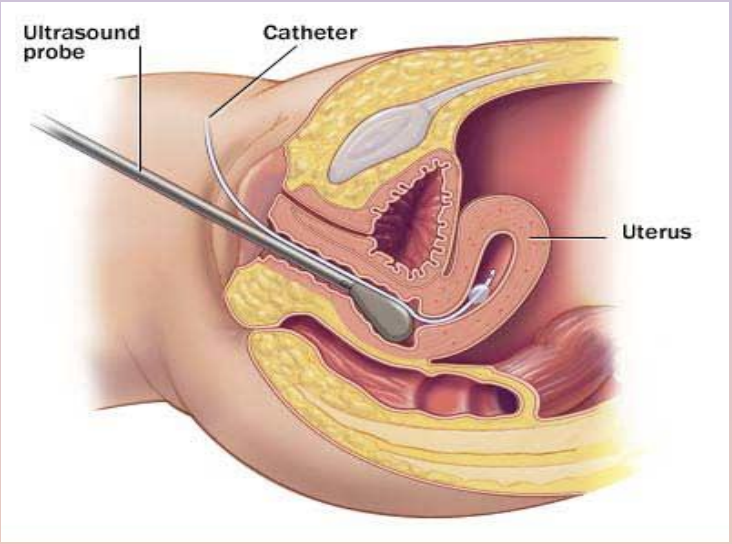
- **Diagnosis:** small narrow uterus.
- **Description:** differential diagnosis : Asherman , DC,TB uterus.

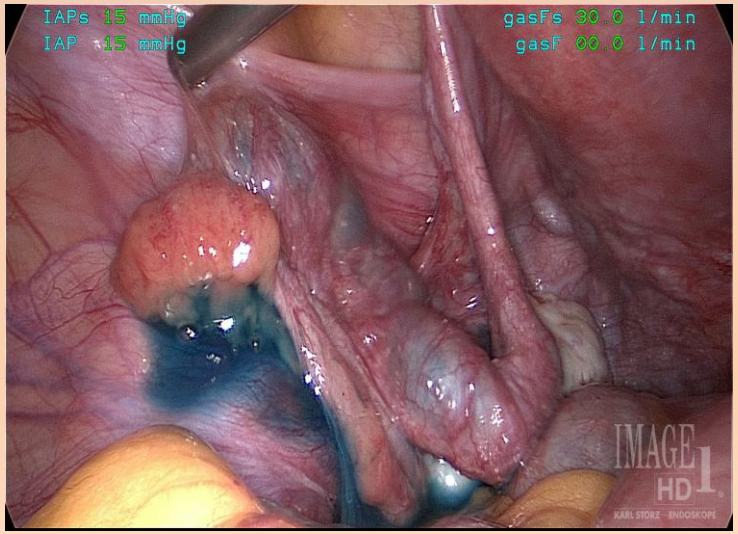
Case 34

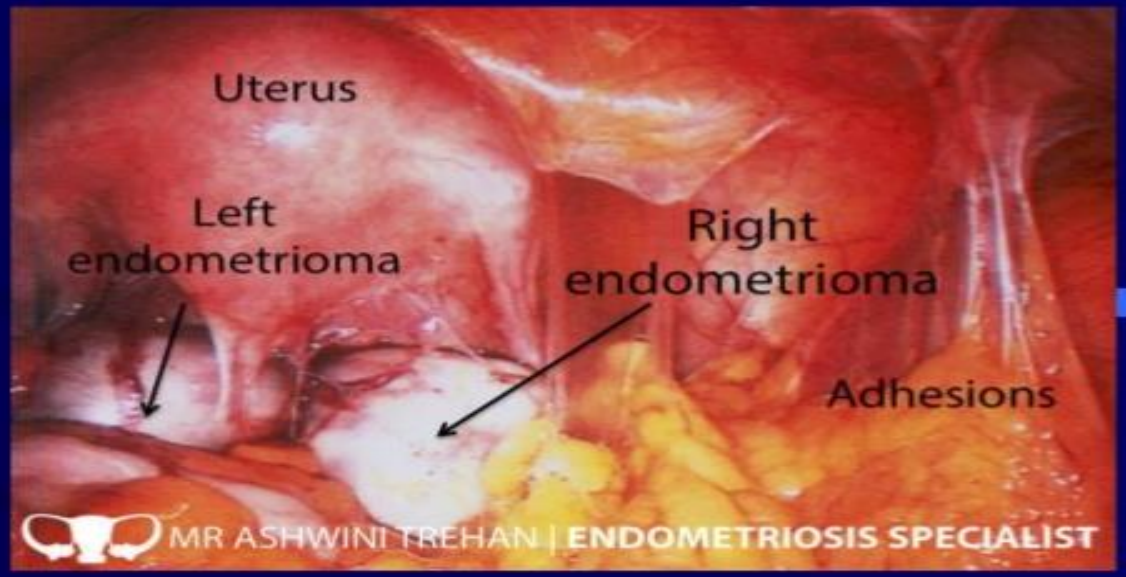


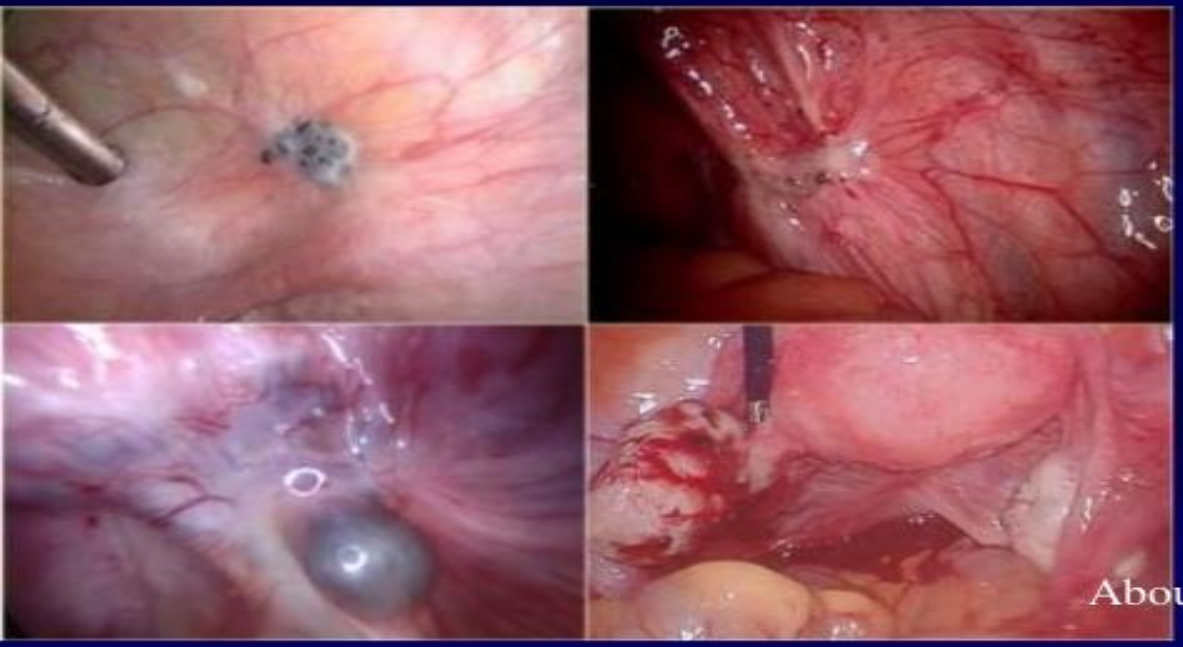
- **Diagnosis:** fallopian tube ligation.
- **Description:** absent uterine tube at both sides.

- **Saline infusion sonography (SIS)** is a test to determine tubal patency using fluid and ultrasound.
- **Laparoscopy** and chromotubation with a dilute solution of methylene blue or indigo carmine (preferred) introduced via the cervix can demonstrate tubal patency or document proximal or distal tubal obstruction.
- The procedure also can identify and correct tubal factors such as fimbrial phimosis or peritubal adhesions, which may not be identified with less invasive methods such as HSG.



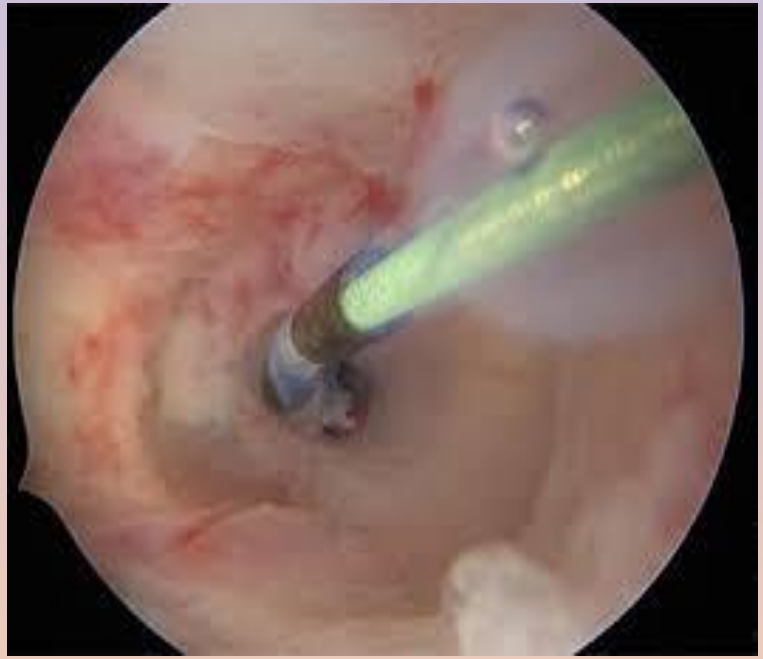






Aboubakr Elnashar

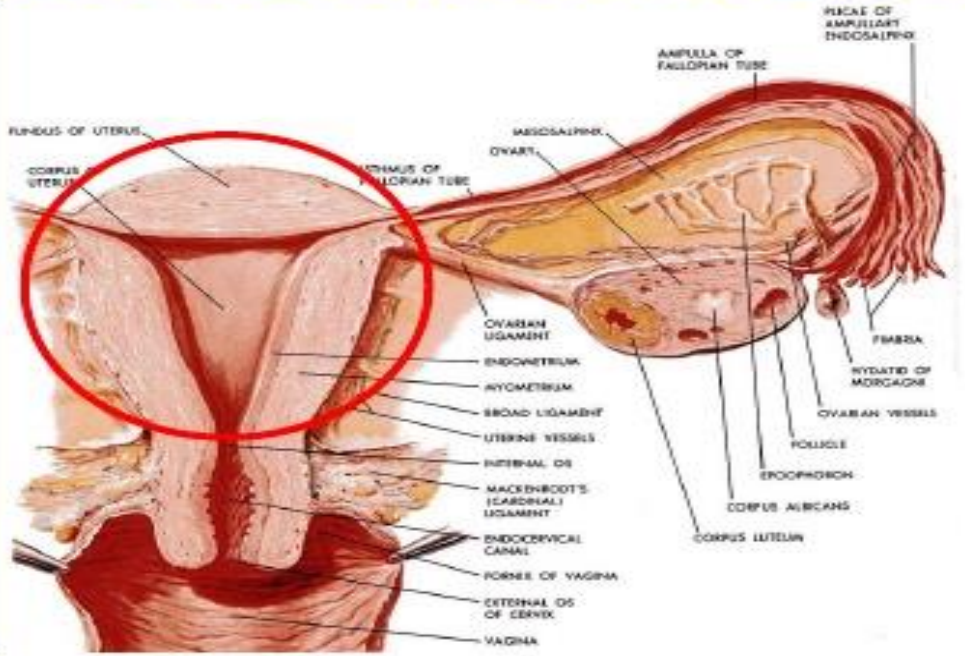
- **Fluoroscopic/hysteroscopic** selective tubal cannulation
- will confirm or exclude any proximal tubal occlusion suggested by HSG or laparoscopy with chromotubation and provides the means for possible correction via recanalization using specialized catheter systems



Chlamydia Antibody Test (CAT)

- The detection of antibodies to Chlamydia trachomatis has been associated with tubal pathology; however, this test has imited clinical utility.
- Compared to laparoscopy, the CAT has lower sensitivity for detection of distal tubal disease

Uterine/endometrial factor



- Anatomical changes (congenital malformations, fibroids, adhesions)
- Functional abnormalities (endometritis, ↓ receptivity)

In women being evaluated for infertility, there are three clinical questions of major interest.

- **Clinical Question 1**
- **Is there an intrinsic abnormality of the endometrium that could explain the couple's infertility** (e.g., **endometrial polyps, submucous leiomyomas, endometritis, hyperplasia, carcinoma**)?
- Much of this information is provided by hysterosalpingogram, hysteroscopy, ultrasound, and laparoscopy, which are increasingly routine procedures for the workup of the infertile patient .

UTERUS

Uterine leiomyomata

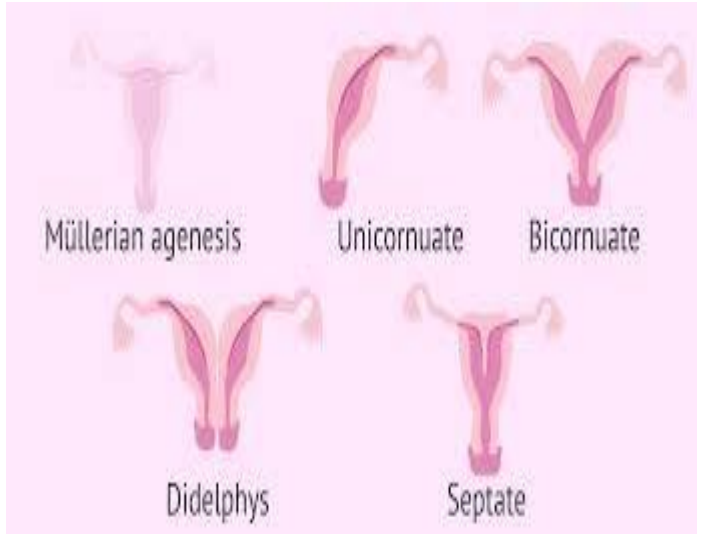
only leiomyomata with a submucosal or intracavitary component were associated with lower pregnancy and implantation rates. The likely mechanism is inhibition to normal implantation

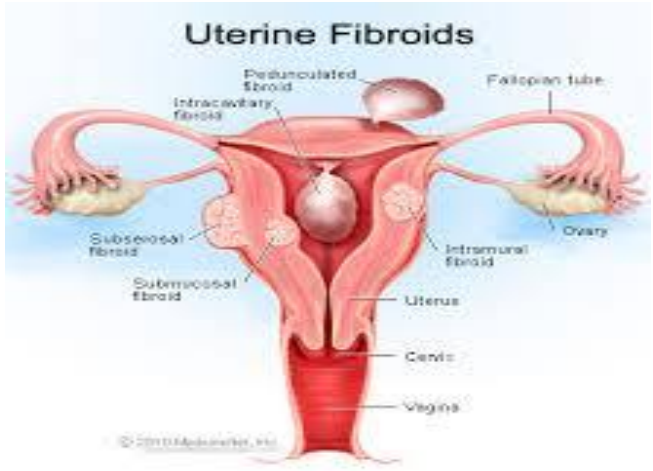
Uterine anomalies

Müllerian anomalies are a significant cause of recurrent pregnancy loss (RPL), with the septate uterus associated with the poorest reproductive outcome

Other structural abnormalities associated with infertility include endometrial polyps, and synechiae from prior pregnancy-related curettage

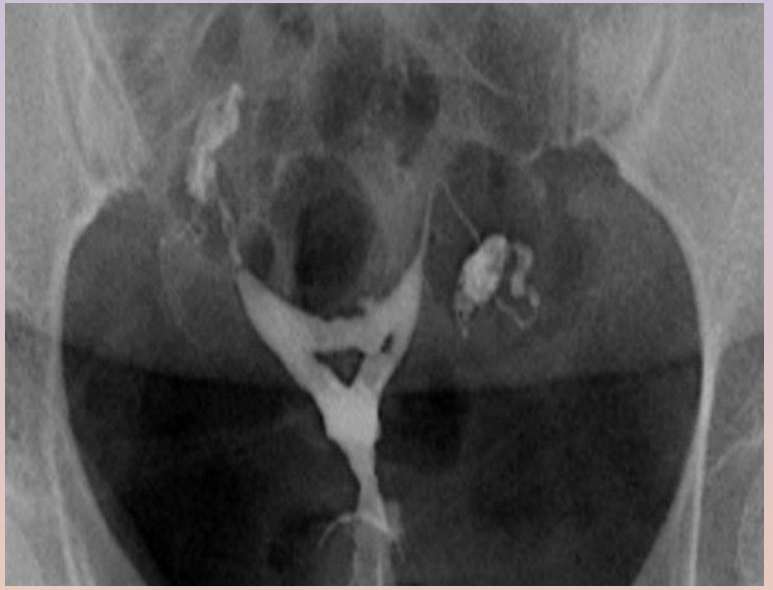
intrauterine adhesions

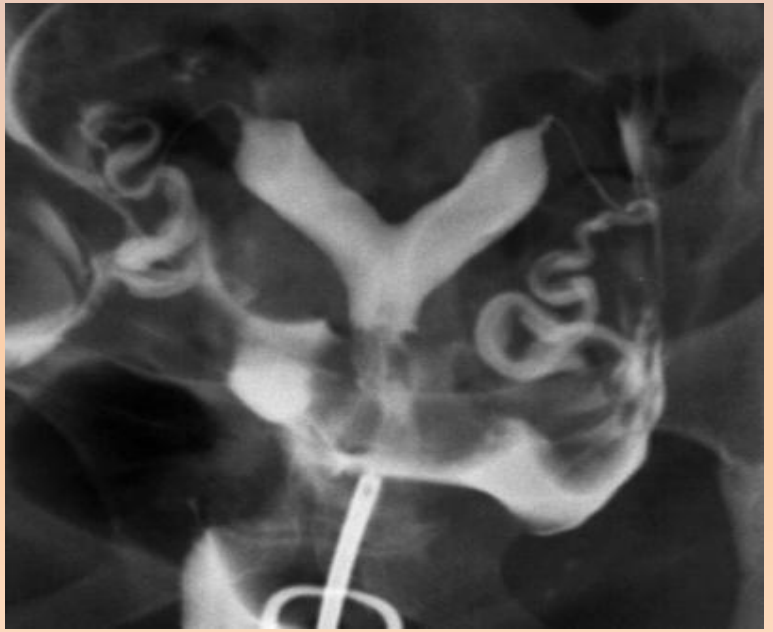




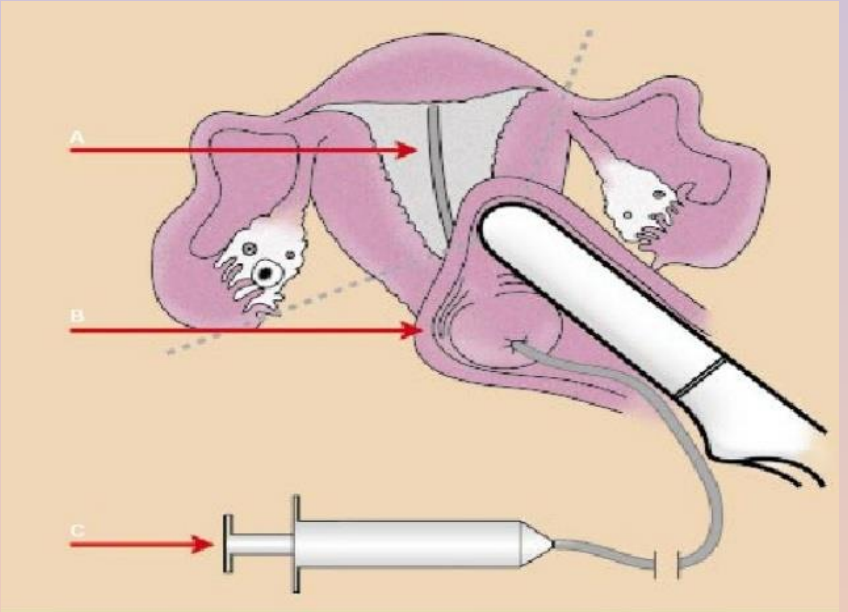
UTERINE ABNORMALITIES

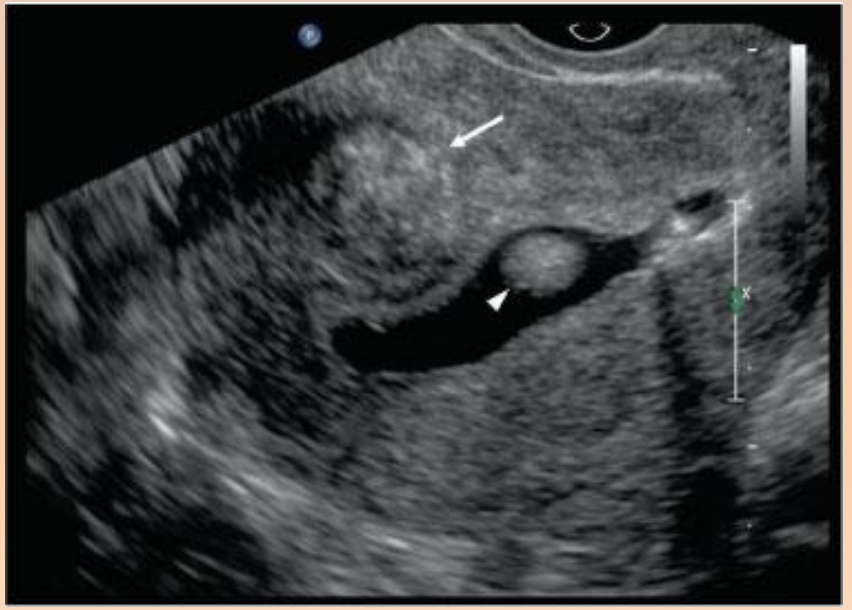
- Abnormalities of uterine anatomy or function are relatively uncommon causes of infertility in women, but should beexcluded.
- Methods for evaluation of the uterus include the following:
- **Hysterosalpingography (HSG)** defines the size and shape of the uterine cavity and can reveal developmental anomalies(unicornuate, septate, bicornuate uteri) or other acquired abnormalities (endometrial polyps, submucous myomas,) having potential reproductive consequences.



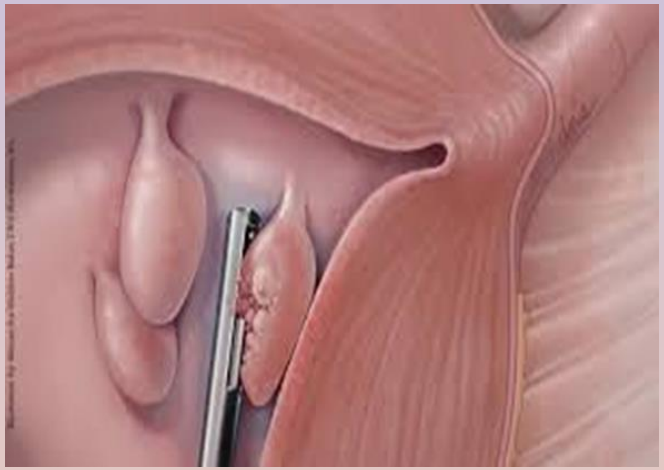


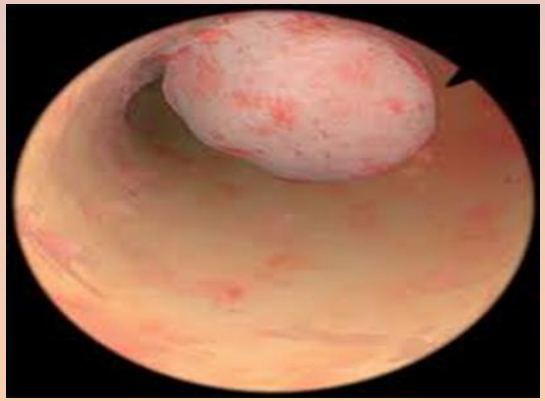
- **Ultrasonography (US)** can be used to diagnose uterine pathology, including myomas
- **Sonohysterography**, involving transvaginal ultrasonography after introduction of saline into the uterine cavity better defines the size and shape of the uterine cavity and for detection of intrauterine pathology (endometrial polyps, submucous myomas, synechiae)

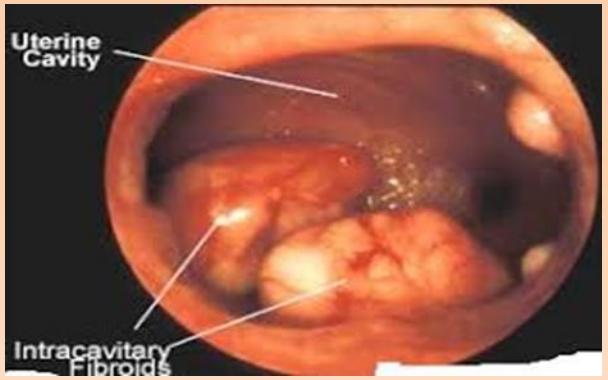




- **Hysteroscopy** is the definitive method for the diagnosis and treatment of intrauterine pathology.
- As it is also the most costly and invasive method for evaluating the uterus, it generally can be reserved for further evaluation and treatment of abnormalities defined by less invasive methods such as HSG and sonohysterography





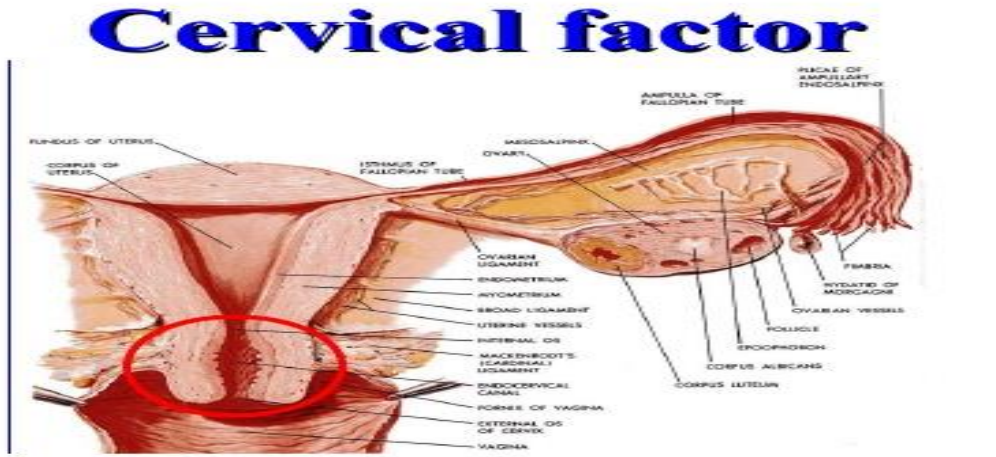


Luteal phase defect — Luteal phase defect (LPD) refers to abnormalities of the corpus luteum that result in inadequate production of progesterone, which is necessary for making the endometrium receptive to implantation. A 2015 committee opinion from the American Society of Reproductive Medicine concluded that "although progesterone is important for the process of implantation and early embryonic development, luteal phase defect (LPD) as an independent entity causing infertility has not been proven" [14]. There are no agreed upon definitions, diagnostic tests, or treatments for LPD [14]. We agree that endometrial dating is not useful for evaluating or guiding treatment of infertile women

CERVICAL FACTORS

Normal midcycle cervical mucus facilitates the transport of sperm

Congenital malformations and trauma to the cervix (including surgery) may result in stenosis and inability of the cervix to produce normal mucus, thereby impairing fertility



- Anatomical changes (DES exposure)
- Infections (TB)
- Changes in mucus characteristics

INHERITED THROMBOPHILIA

- Inherited thrombophilias do not appear to be related to unexplained infertility

- A large retrospective study reported no significant association with common thrombophilias, including factor V Leiden and lupus anticoagulant, and diminished in vitro fertilization success

- Thus, neither screening for thrombophilias nor treating them is advised in cases of repeated infertility treatment failure

IMMUNE FACTORS

Antiphospholipid syndrome

Antiphospholipid syndrome may lead to immunological rejection of the early pregnancy or placental damage

Evaluation for this disorder depends upon the patient's medical and family history and whether infertility is related to recurrent early pregnancy failure (work-up indicated) or failure to conceive (work-up not indicated)

Antibodies unrelated to APS – An increased frequency of abnormal immune test results in women with early reproductive failure has been reported repeatedly; however, the most rigorous studies have not proven a cause and effect between these phenomena [24]. Immune testing of infertile couples in clinical practice is not supported by existing data and treatments administered to address abnormal results on immunological testing solely for the purpose of improving fertility have not been proven to be beneficial and may cause harm.

Women with some autoimmune diseases are at increased risk of infertility unrelated to direct effects of these antibodies on fertilization and implantation

For example, premature ovarian failure has also been described in women with systemic lupus erythematosus and myasthenia gravis

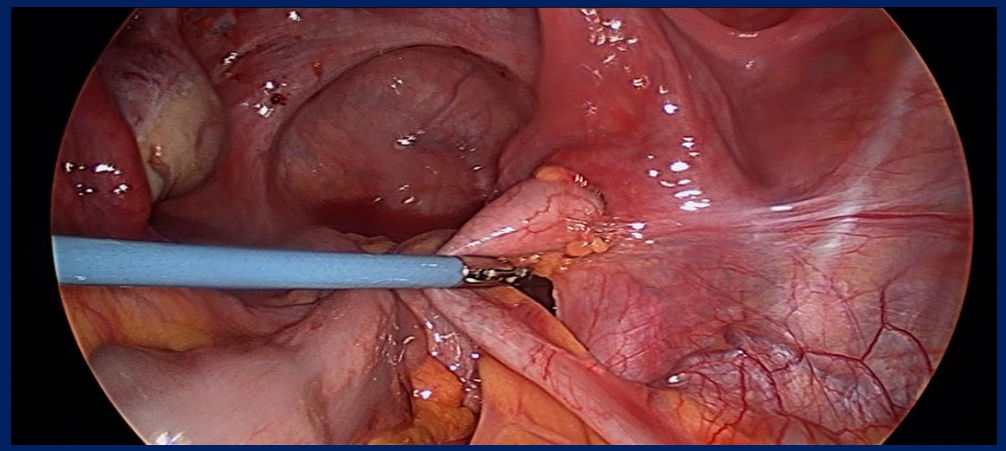
Autoimmune oophoritis may occur as part of type I and type II syndromes of polyglandular autoimmune failure, which are associated with autoantibodies to multiple endocrine and other organs

ENDOMETRIOSIS

Mechanisms which decrease fertility in women with endometriosis include

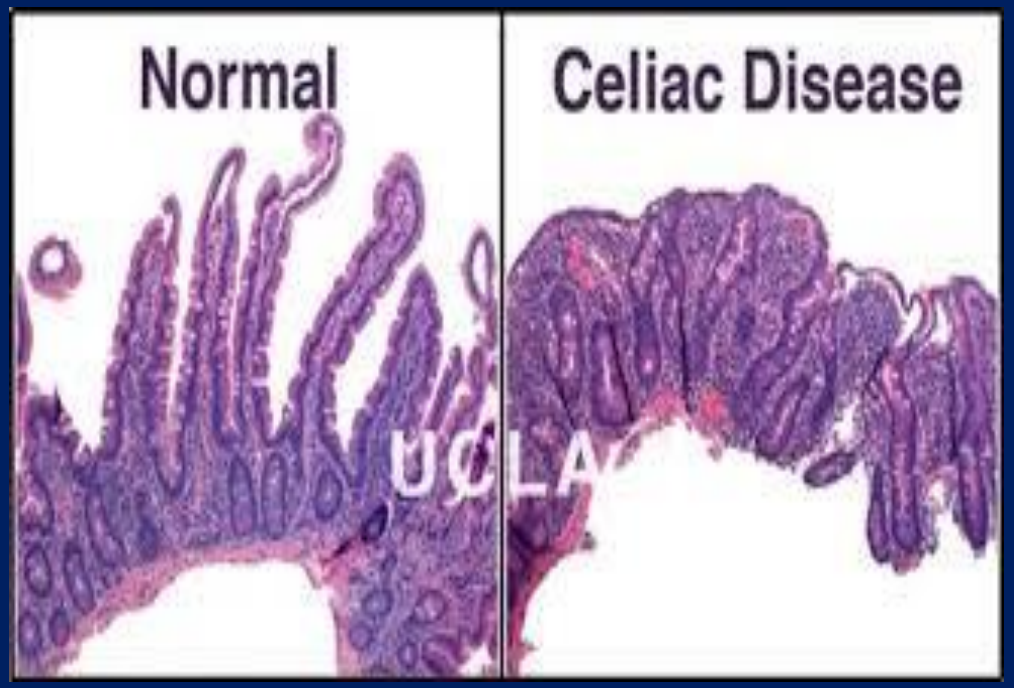
- anatomic distortion from pelvic adhesions
- damage to ovarian tissue by endometrioma formation and surgical resection
- the production of substances such as cytokines and growth factors

which impair the normal processes of ovulation, fertilization, and implantation



Celiac disease

- women with untreated celiac disease may have an increased frequency of reproductive abnormalities, including infertility, miscarriage, and intrauterine growth restriction



GENETIC CAUSES

— Infertile couples have been shown to have a higher prevalence of karyotype abnormalities (trisomies, mosaics, translocations, etc) than the general population [26]. The frequency varies according to the cause of infertility and clinical history. The most common aneuploidies associated with infertility are 45X (Turner syndrome) in women and 47XXY (Klinefelter syndrome) in men.

GENETIC CAUSES

- Individual genes that affect fecundity have been identified, including *KAL1* (Kallmann's syndrome) [27], GnRH receptor [28,29], FSH receptor [30], beta subunit of FSH [31], LH receptor [32], *FMR1* (fragile X syndrome) [33], *SF1*, *DAX1* [34], *LEP* (leptin) [35], *LEP* receptor [36], *GPR54* , *FGFR1* [39], and *TUBB8* [40]. *TUBB8* mutations are unique in that they impact only oocytes. *TUBB8* mutations disrupt microtubule function during oocyte division and thereby arrest human oocyte maturation and prevent fertilization [40]. Of these genes, clinical testing is available for abnormalities of *FMR1,* which causes fragile X syndrome

Semen analysis — Semen analysis is the key laboratory assessment of the male partner of an infertile couple. The standard semen analysis consists of the following:

- Semen volume and pH
- Microscopy for:
- Sperm concentration, count, motility, and morphology
- Debris and agglutination
- Leukocyte count
- Immature germ cells

The semen sample should be collected after two to seven days ejaculatory abstinence. If possible, the patient should collect the sample by masturbation at the doctor's office. If not possible, then the sample may be collected at home and delivered to the laboratory within an hour of collection.

Because of the marked inherent variability of sperm concentrations in semen samples, **at least two samples** should be collected at least one week apart. The semen analysis should be performed using standardized methods, preferably those described in the World Health Organization (WHO) Laboratory Manual for the Examination and Processing of Human Semen [13]. In addition, the laboratory should employ internal quality control measures and participate in external quality control programs available from national andrology, clinical chemistry, and pathology societies

Reference limits — The WHO has published lower reference limits for semen analyses [17]. The following parameters represent the generally accepted 5th percentile (lower reference limits and 95% CIs in parentheses), derived from a study of over 1900 men whose partners had a time to pregnancy of ≤12 months [17]:

- Volume – 1.5 mL (95% CI 1.4-1.7)
- Sperm concentration – 15 million spermatozoa/mL (95% CI 12-16)
- Total sperm number – 39 million spermatozoa per ejaculate (95% CI 33-46)
- Morphology – 4 percent normal forms (95% CI 3-4), using "strict" Tygerberg method [13]
- Vitality – 58 percent live (95% CI 55-63)
- Progressive motility – 32 percent (95% CI 31-34)
- Total (progressive and nonprogressive) motility – 40 percent (95% CI 38-42)


Thank you