

# PRIMINARY EVALUATION OF THE INFERTILE COUPLE

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# Infertility

- ▶ Infertility is defined as 1 year of regular unprotected intercourse without conception.
- ▶ term subfertility is used interchangeably to describe women or couples who may not be sterile but exhibit decreased reproductive efficiency
- ▶ Approximately 85-90% of healthy young couples conceive within 1 year, most within 6 months.

# Infertility

- ▶ Infertility therefore affects approximately 10-15% of couples and represents an important part of clinical practice.
- ▶ the overall incidence of infertility does not seem to have increased over the past three decades.
- ▶ the evaluation and treatment of infertility have changed dramatically during the same period.

# THE EPIDEMIOLOGY OF INFERTILITY

- ▶ The general fertility rate (births per 1,000 women aged 15-44) in 2015 was 62.5, 8% lower than in 1990 (70.9/1,000), 25% lower than in 1970 (87.9/1,000), and 41% lower than in 1950 (106.2/1,000) during the postwar “baby boom.

# THE EPIDEMIOLOGY OF INFERTILITY

- ▶ Greater interest in advanced education and careers among women
- ▶ Later marriage and more frequent divorce
- ▶ Improvements in contraception and access to family planning services
- ▶ Delayed childbearing
- ▶ Decreased family size

# THE EPIDEMIOLOGY OF INFERTILITY

- ▶ increasing age at first birth and declining fertility rates combined to result in fewer births per woman.
- ▶ the total fertility rates in most industrialized countries are inadequate even to ensure replacement of the population.<sup>17</sup>

# THE EPIDEMIOLOGY OF INFERTILITY

- ▶ The array of infertility services, and their availability, has increased dramatically over the last 25 years
- ▶ As infertility has become more visible, and more socially acceptable, couples have become more comfortable to seek evaluation and treatment.

# GUIDING PRINCIPLES FOR EVALUATION AND TREATMENT OF INFERTILITY

- ▶ the evaluation of infertility should focus on the couple and not on one or the other partner
- ▶ both partners should be present during office visits.
- ▶ allow each partner to express her or his own opinion and be able to ask questions directly

# The four basic goals of management of infertility are:

- ▶ To identify and to correct specific causes of infertility, when possible. With proper evaluation and treatment, the majority of women will achieve pregnancy
- ▶ To provide accurate information and to dispel the misinformation commonly gained from friends, mass media, and the Internet.

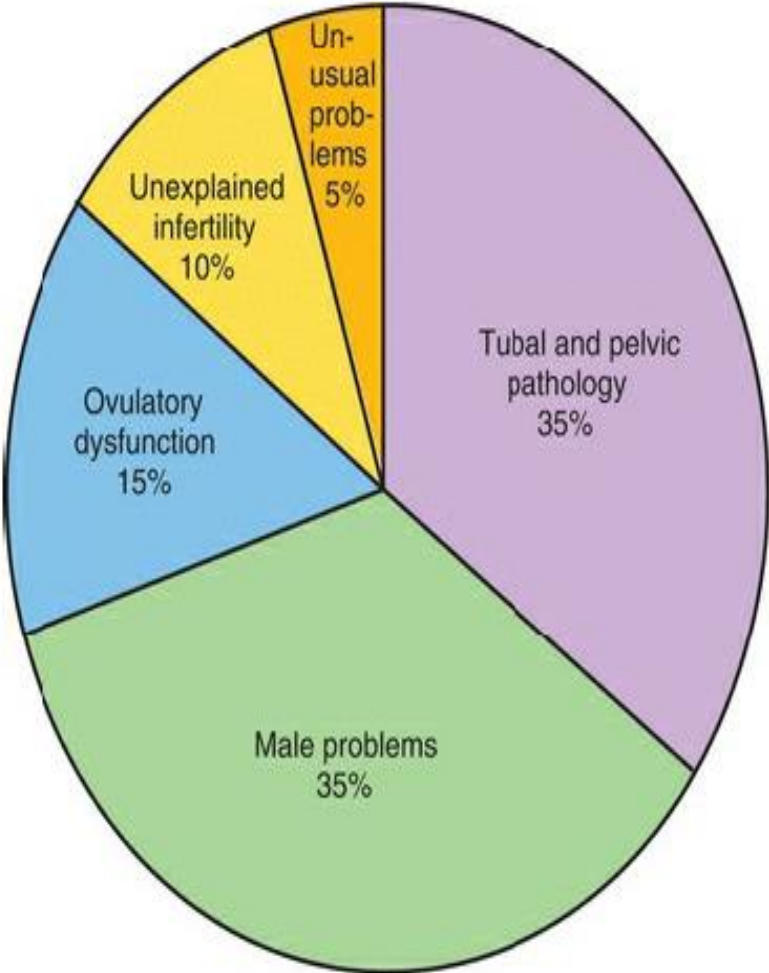
# The four basic goals of management of infertility are:

- ▶ To provide emotional support during a trying time.
- ▶ To guide couples failing to conceive with other forms of treatment to alternatives, including IVF, the use of donor gametes (oocytes or sperm), and adoption, and to help those who reject or fail treatment to come to closure.

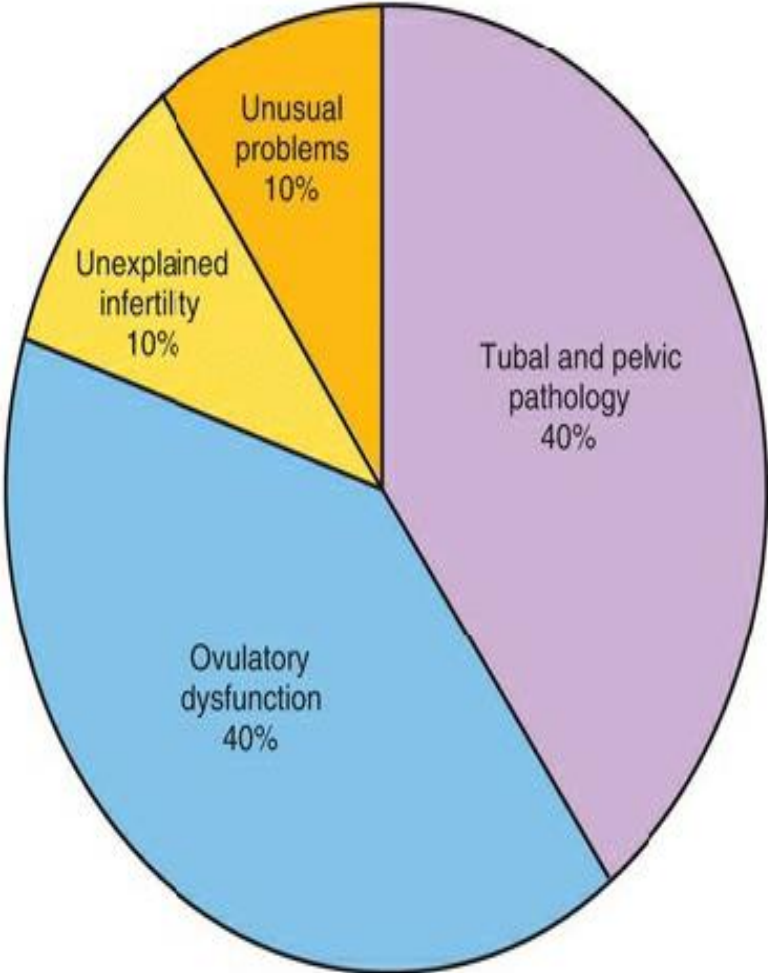
# Causes of Infertility

- ▶ ovulatory dysfunction (20-40%)
- ▶ tubal and peritoneal pathology (30-40%)
- ▶ male factors (30-40%)
- ▶ uterine pathology
- ▶ In about 40% of cases disorders are found in both the male and female

# Causes of Infertility



Couples



Women

# Indications for Evaluation

- ▶ Evaluation should be offered to all couples who have failed to conceive after a year or more of regular unprotected intercourse

# Earlier evaluation is justified

- ▶ irregular or infrequent menses
- ▶ history of pelvic infection
- ▶ surgery or endometriosis,
- ▶ having a male partner with known or suspected poor semen quality
- ▶ after 6 months of unsuccessful effort for women over the age of 35 years.<sup>1,3</sup>

# History and Examination of the Female Partner

- ▶ History
- ▶ Obstetric history including gravidity, parity, pregnancy outcomes, and associated complications.
- ▶ Menstrual history including cycle length and characteristics and onset and severity of dysmenorrhea.
- ▶ Coital frequency and sexual dysfunction.
- ▶ Duration of infertility and results of any previous evaluation and treatment.
- ▶ Medical and surgical history, including episodes of pelvic inflammatory disease or exposure to sexually transmitted infections.
- ▶ Previous abnormal cervical cancer screening results and subsequent treatment.
- ▶ Current medications and allergies.
- ▶ Occupation and use of tobacco, alcohol, and other drugs.
- ▶ Family history of birth defects, mental retardation, early menopause, or reproductive failure.
- ▶ Symptoms of thyroid disease, pelvic or abdominal pain, galactorrhea, hirsutism, or dyspareunia.

# Physical Examination

- ▶ Weight and BMI.
- ▶ Thyroid enlargement, nodule, or tenderness.
- ▶ Breast secretions and their characteristics.
- ▶ Signs of androgen excess.
- ▶ Pelvic or abdominal tenderness, organ enlargement, or mass.
- ▶ Uterine size, contour, position, and mobility.
- ▶ Vaginal or cervical abnormality, secretions, or discharge.
- ▶ Mass, tenderness, or nodularity in the adnexa or cul-de-sac

# Evaluation

- ▶ The initial evaluation is also used to counsel patients regarding preconception care, lifestyle changes (including avoidance of smoking and toxic exposure), and to identify situations requiring specific care, such as history of genetic diseases or consanguinity. Cessation of smoking is essential not only for general health, but also to improve fertility

# Evaluation

- ▶ Women should also be offered testing for rubella status
- ▶ Women should also be offered testing for rubella status
- ▶ Both partners should be tested for their HIV status and hepatitis B and C serology
- ▶ Regular intake of folic acid is advised

# FEMALE INVESTIGATION

- ▶ **Baseline investigations :**
- ▶ Ovulatory function
- ▶ ovarian reserve
- ▶ uterine cavity, and tubal patency.

# Ovulatory function

- ▶ Regular menstrual cycle, occurring at intervals of 21-35 days is usually indicative of normal ovulation
- ▶ In women with oligomenorrhea or amenorrhea, no formal evaluation is needed to establish a diagnosis of ovulatory dysfunction

# Tests

- ▶ Basal Body Temperature
- ▶ Serum Progesterone Concentration
- ▶ Urinary LH Excretion
- ▶ Endometrial Biopsy
- ▶ Transvaginal Ultrasonography

# Tests

- ▶ For practical purposes, menstrual history may be all that is required in women with regular cycles in order to confirm ovulation. Still, NICE guidelines do recommend measuring mid-luteal progesterone in women undergoing infertility investigation even in the presence of regular cycles.

# *Other hormonal tests*

- ▶ **Hormonal tests include evaluation of:**
- ▶ ovarian reserve
- ▶ prolactin measurement
- ▶ thyroid function.
- ▶ Women with signs and symptoms of hyperandrogen-ism require further investigations (serum testosterone,  $\delta$ 4-androstenedione, DeHydroEpiAndrosterone-Sulfate (DHEA-S) and 17-hydroxy-progesterone) to rule out the presence of late-onset congenital adrenal hyperplasia, Cushing syndrome, or androgen-producing tumors.

# Ovarian reserve

- ▶ Ovarian reserve evaluation is an essential component in the infertility workup.
- ▶ The main goal is to evaluate the fertility potential and predict ovarian response to controlled ovarian stimulation.
- ▶ It helps clinicians to choose the optimal stimulation strategy and to avoid iatrogenic complications, such as ovarian hyperstimulation syndrome
- ▶ Their value is limited in the prediction of ongoing pregnancy, both for spontaneous conceptions or those achieved by ART
- ▶ Age remains the best predictor of pregnancy following *in vitro* fertilization

# The main tests for ovarian reserve

- ▶ *Day-3 serum FSH and E2 :*
- ▶ Serum FSH concentration is best obtained during the early follicular phase (cycle days 2-4).
- ▶ FSH levels greater than 10 IU/L (10-20 IU/L) have high specificity (80-100%) for predicting poor response to stimulation
- ▶ When the basal FSH is normal and the estradiol concentration is elevated (>60-80 pg/mL), the likelihood of poor response to stimulation is increased and the chance for pregnancy is decreased.

# The main tests for ovarian reserve

## ▶ *Antral follicle count :*

- ▶ AFC has been described as the sum of all follicles 2-10 mm in the largest diameter measured by transvaginal US
- ▶ It is a direct marker of ovarian reserve.
- ▶ An AFC lower than 4 is predictive of a low response

One of the three criteria of PCOS in the Rotterdam criteria is the presence of 12 or more antral follicles of 2-9 mm per ovary

# The main tests for ovarian reserve

- ▶ *Anti-Mullerian hormone :*
- ▶ AMH is a dimeric glycoprotein member of the TGF- $\beta$  superfamily and is produced in ovaries
- ▶ The strongest staining of AMH is observed in pre-antral and small antral follicles
- ▶ Since cyclic variation of AMH is minimal blood sampling for AMH can be obtained at any time during the cycle.
- ▶ AMH seems to demonstrate less intra- and inter- cycle variability than AFC
- ▶ AMH levels greater than 3.5 ng/mL are predictive of a high ovarian response and AMH <0.5–1.1 ng/mL is predictive of low response

# Cervix :

## ▶ Cervix :

- ▶ The postcoital test (PCT) evaluates motile sperm in the cervical mucus around ovulation time and within hours following intercourse.
- ▶ it has poor inter- and intra-observer reproducibility
- ▶ There is no consensus on the definition of cervical infertility, and current treatments for unexplained infertility are able to overcome cervical factors

# Uterus :

- ▶ Intrauterine abnormalities including endometrial polyps, submucosal myoma, adhesions, or a uterine septum interfering with fertility and compromising pregnancy rates in assisted reproduction.
- ▶ Two-dimensional transvaginal US :
- ▶ The first-line diagnostic tool to evaluate uterine cavity is two-dimensional transvaginal US
- ▶ It is inexpensive, easy to perform, and well tolerated by patients
- ▶ US has less diagnostic value in differentiating submucosal fibroids in the presence of multiple fibroids, endometrial polyps within a thick endometrium, and synechiae or uterine malformations.

# Uterus :

## ▶ Hysterosalpingography (HSG) :

- ▶ Evaluates tubal patency and, to a certain extent, is an assessment of the uterine cavity

## ▶ Hysterosonography (sonohysterography):

- ▶ Is a combination of US with saline or contrast media infusion into the uterine cavity.
- ▶ As with US, it is more precise for diagnosing polyps or submucosal fibroids than endometrial hyperplasia or structural abnormalities

# Uterus :

- ▶ Three-dimensional hysterosonography :
- ▶ Three-dimensional hysterosonography could also be performed and seems to be comparable with hysteroscopy for diagnosing intrauterine lesions
- ▶ Hysteroscopy :
- ▶ Hysteroscopy remains the most accurate test and is
- ▶ considered the gold

standard for evaluation of the uterine cavity Since hysteroscopy is an invasive method for evaluation of the uterine cavity, it is usually reserved for further evaluation and treatment of already-suspected anomalies using imaging techniques

# Uterine anomalies

- ▶ Laparoscopy combined with hysteroscopy is also accurate, but is invasive.
- ▶ MRI is an accurate and noninvasive test, but it is costly
- ▶ Three-dimensional US seems to be a good compromise, as it is highly correlated with the results of MRI, laparoscopy, and hysteroscopy, particularly when performed during the luteal phase, as the thick endometrial lining enhances cavity visualization

# *Fallopian tubes*

- ▶ Hysterosalpingography :
- ▶ HSG is radiographic evaluation of the fallopian tubes
- ▶ Contraindications to HSG include contrast allergy, pregnancy, and active pelvic infection.
- ▶ HSG findings of “proximal tubal occlusion” are usually due to tubal spasm, collection of debris, or a mucus plug inside the proximal tubes. Such findings should be followed up with additional tests such selective tubal catheterization.
- ▶ HSG is more specific for detecting distal as opposed to proximal occlusion

# *Fallopian tubes*

- ▶ Hysterosalpingo-contrast sonography :
- ▶ HyCoSy shows intratubal flow of contrast media
- ▶ The presence of fluid in the cul-de-sac after uterine instillation implies patency of at least one tube
- ▶ Pain induced by HyCoSy and its complications are comparable to HSG

# *Fallopian tubes*

- ▶ Laparoscopy :
- ▶ Laparoscopy with chromopertubation has long been considered as the “gold standard” for evaluating tubal patency
- ▶ Laparoscopy is indicated when there is evidence or strong suspicion of endometriosis, pelvic/adnexal adhesions, or significant tubal disease requiring treatment.
- ▶ It is an invasive procedure that requires general anesthesia.
- ▶ Its advantages include the feasibility to diagnose and treat conditions

# MALE INVESTIGATION

- ▶ Basic male investigation begins with a detailed history and physical examination.
- ▶ Semen analysis and a serum hormonal profile represent the first-line laboratory investigations.
- ▶ More importantly, a thorough male fertility evaluation may reveal serious associated conditions including testis cancer, osteoporosis/osteopenia, and genetic and hormone disorders that can have significant health consequences or even be life threatening.

# MALE INVESTIGATION

- ▶ History :
- ▶ A general history should include the developmental history such as congenital malformation of the genitalia, cryptorchidism , and delayed onset of puberty.
- ▶ Previous history of herniorrhaphy, particularly in childhood, may result in inadvertent damage to the vas deferens that has not been recognized.
- ▶ A history of mumps orchitis (par- ticularly in adolescence)
- ▶ Sexually transmitted infections, genitourinary surgeries, instrumentation, or trauma should be obtained
- ▶ Symptoms of the lower urinary tract and erectile and ejaculatory functions should also be carefully reviewed.

# MALE INVESTIGATION

- ▶ A systematic review of related organ system function such as pulmonary disease and upper respiratory infections may suggest genetic conditions such as Young's syndrome, Kartagener's syndrome (immotile cilia syndrome; primary ciliary dyskinesia), or cystic fibrosis (CF).
- ▶ A history of a metabolic or neurological condition may be related to impaired erectile and ejaculatory function.
- ▶ History of gonadotoxic treatment should also be recorded.
- ▶ Use of medication, alcohol, drugs, and occupational and environmental exposure to toxins such as heat and chemicals that can act as endocrine disruptors are elements to be recorded as well.
- ▶

# MALE INVESTIGATION

- ▶ Physical examination :
- ▶ A thorough physical examination should focus on general signs, such as secondary sex characteristics that reflect normal androgenization (hair distribution, absence of gynecomastia, and skeletal muscle development), and on the genitalia.
- ▶ Genital examination includes localization of the penile urethral meatus and palpation of the testes for their presence, size, and consistency.
- ▶ Small testes are related to testicular dysfunction or hypogonadism.
- ▶ Congenital bilateral absence of vas deferens (CBAVD) suggests the presence of mutation of the CF transmembrane conductance regular gene (*CFTR*).
- ▶ Examination of the spermatic cord in the upright position is important to evaluate the presence of varicoceles

# Laboratory investigations

## ▶ Semen analysis :

- ▶ The first-line laboratory investigation for male infertility includes semen analysis performed according to the WHO criteria
- ▶ Bacteriological semen analysis is usually done at the same time in order to explain potential semen anomalies, to screen for *C. trachomatis*, and to identify and treat an infection that could impair ART.
- ▶ abnormal semen analysis results should be repeated at least one month later to confirm the diagnosis
- ▶ Semen samples should be ideally collected by masturbation after two to five days of abstinence

# Laboratory investigations

- ▶ Semen analysis assesses parameters including volume, pH, sperm concentration, vitality, motility, and morphology. The main reference values of semen analysis according to the WHO are summarized in [Table](#)

**Table 37.1** Reference values of semen analysis according to the World Health Organization

<u>Criteria</u>	<u>Reference value</u>
Volume	≥1.5 mL
pH	≥7.2
Total sperm number	≥39 million/ejaculate
Sperm concentration	≥15 million/mL
Total motility	≥40%
Progressive motility	≥32%
Normal morphology	≥4%
Vitality	≥58%

# Laboratory investigations

- ▶ Aspermia is the absence of semen and can be related to retrograde ejaculation or anejaculation due to psychological or neurological causes.
- ▶ In the case of retrograde ejaculation, a post-orgasm urine analysis may be performed, with specific preparation
- ▶ A pH of less than 7 in a sample with low volume and azoospermia strongly suggests ejaculatory duct obstruction or CBAVD.
- ▶ severe oligozoospermia, the limit of 5 million/mL is generally accepted
- ▶ Sperm motility is graded as progressive motility (PR; spermatozoa moving actively regardless of the speed), non-progressive motility (NP; motility with an absence of progression), and immotile
- ▶ While we have the ability to overcome abnormally motile sperm with ARTs, the importance of progressive sperm motility in fertilizing oocytes *in vivo* has long been established

# Endocrine tests

- ▶ If the semen analysis indicates a low number or concentration of sperm, or in cases of male sexual dysfunction, further endocrine tests should be requested
- ▶ Serum FSH and total testosterone measurements should be performed in all cases of oligozoospermia. This will help distinguish between pituitary-hypothalamic axis dysfunction, testicular dysfunction, and reproductive tract obstruction
- ▶ Additional hormonal evaluation such as LH, prolactin, and TSH should be requested if the clinical findings suggest a specific pathology
- ▶ Low levels of FSH, LH, and testosterone in the context of low sperm concentrations suggest hypogonadotropic hypogonadism.
- ▶ In the case of complete testicular failure, FSH and LH will be elevated whereas testosterone will be normal or low.

# Genetic testing

- ▶ Males having abnormal spermatogenesis related to testicular failure, such as in NOA or severe oligozoospermia (<5 million/mL), are at increased risk for having genetic abnormalities compared to fertile men
- ▶ Genetic testing including karyotype analysis and Y-chromosome microdeletion is recommended
- ▶ If the karyotype is abnormal, there is an increased risk of sperm chromosomal aneuploidy, and genetic counseling including preimplantation genetic diagnosis should be discussed with the couples prior to assisted reproduction.

# Obstructive azoospermia

- ▶ CBAVD is a common cause of primary OA in healthy men with no prior history of genitourinary disorders. There is a strong association between CBAVD and mutations of the *CFTR* gene
- ▶ . CF is a serious autosomal recessive condition. Almost all men with CF exhibit CBAVD
- ▶ In summary, men with NOA or severe oligozoospermia should be offered karyotype evaluation and Y chromosome analysis
- ▶ CBAVD/CUAVD further warrants *CFTR* mutation screening and genetic counseling

# CONCLUSION

- ▶ Infertility is a difficult situation for a couple. Basic investigations beginning with a detailed history and physical examination are the first step of infertility management
- ▶ Each member of the couple should undergo basic infertility investigations including evaluation of the uterine cavity, the fallopian tubes, ovarian function and reserve, and semen analysis. These investigations could create anxiety
- ▶ Our goal as physicians is to provide education, counseling, and assistance, including emotional support, during the initial investigations and later during the treatment