Female Infertility

- Infertility is defined as 1 year of regular unprotected intercourse without conception.
- Infertility therefore affects approximately 10–15% of couples.

THE EPIDEMIOLOGY OF INFERTILITY IN THE UNITED STATES

- The overall long-term decline in the US birth and fertility rates has been attributed to several factors:
- 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.

AGING AND FERTILITY

- Overall, fertility rates are 4–8% lower in women aged 25–29 years, 15–19% lower in those aged 30–34, 26–46% lower in women aged 35–39, and as much as 95% lower for women aged 40–45 years.
- In the 2015 US national summary, the live birth rate per embryo transfer was 46.5% for women under age 35, 38.4% for ages 35–37, 27.4% for ages 38–40, 15.5% for ages 41–42, and 6.6% for women aged 43–44 years, despite higher number of embryos being transferred to older women.

- The age-related decline in ART live birth rates reflects not only decreasing fertility but also increasing pregnancy wastage.
- Just as fertility decreases with increasing age, the incidence of clinically recognized miscarriage rises as age advances. Miscarriage rates in natural conception cycles are generally low before age 30 (7–15%) and rise with age, only slightly for ages 30–34 (8–21%), but to a greater extent for ages 35–39 (17–28%) and ages 40 and older (34–52%)

Physiology of Reproductive Aging

Follicular Depletion

- the number of oocytes peaks around the 20th week of gestation when approximately 6–7 million oocytes.
- The number of oocytes declines to 1–2 million at birth and to 300,000–400,000 by puberty.
- Over the next 35–40 years of reproductive life, only about 400 oocytes will ovulate, the rest being lost through atresia.
- By age 40, the number of follicles shrinks to approximately 25,000, and at menopause, there remains less than 1,000 follicles

Endocrinology of Reproductive Aging

- Toward the end of the reproductive period, serum follicle-stimulating hormone (FSH) levels begin to rise, while luteinizing hormone (LH) concentrations remain unchanged.

This occurs before any discernible change in menstrual regularity.

- **The bulk of available evidence indicates that the progressive increase in FSH concentrations associated with reproductive aging results from a progressive decrease in the levels of feedback inhibition** from **the smaller cohorts of follicles recruited from a shrinking follicular pool.**
- Circulating follicular phase inhibin B levels (derived primarily from smaller antral follicles) decrease as or even before FSH concentrations begin to increase.
- Inhibin A levels also decline, but only in the later stages of reproductive aging, after the onset of menstrual Irregularity. Both inhibins selectively inhibit pituitary FSH secretion.

- As age and FSH levels increase, the follicular phase becomes shorter .LH levels and luteal phase duration remain unchanged.
- As the follicular phase shortens, estradiol levels rise earlier, suggesting that higher FSH levels stimulate more rapid follicular development.
- **However, careful studies have shown that the earlier rise in estradiol levels results not from accelerated follicle growth, but from advanced follicular development at the beginning of the cycle and earlier selection of the dominant follicle.**

- The earlier increase in follicular phase FSH level also frequently results in more than one dominant follicle, explaining the higher prevalence of dizygotic twinning in older cycling women.
- Reproductive aging already is quite advanced when the first clinical sign appears.

- The menopausal transition begins at an average age of 46 years, but can arrive as early as age 34 and as late as age 54 Years.
- loss of menstrual regularity to menopause is relatively fixed, spanning approximately 5- 6 years.
- The age of menopause, recognized only in retrospect, averages 51 years, but ranges widely between ages 40 and 60 years.

Genetics of Reproductive Aging

- **Approximately 10% of women become menopausal by the age of 45, probably because they were endowed with a smaller than average ovarian follicular pool that is functionally depleted at an earlier age.**
- Moreover, women who repeatedly respond poorly to exogenous gonadotropin stimulation also tend to have an earlier menopausal transition, suggesting their poor response.

The Aging Follicle and Oocyte

- observations in stimulated cycles suggest that aging follicles also become progressively less sensitive to gonadotropin stimulation.

As age increases, the total dose and duration of treatment required to stimulate multiple follicular development increase.

The rate of rise and the peak in estradiol levels decrease, reflecting the smaller cohorts of follicles that can be recruited.

- Older cycling women ovulate as regularly and more frequently than younger women.
- Their rising FSH levels apparently compensate quite effectively for any decrease in follicular sensitivity to gonadotropin stimulation.
- **The available evidence indicates that both the age-related decline in female fertility and the increase in risk of miscarriage can be attributed to an increase in the proportion of abnormal oocytes in an aging and shrinking follicular pool.**

- As the number of follicles decreases, oocyte quality also declines, primarily because of an increase in meiotic nondisjunction, resulting in an increasing rate of oocyte and embryo aneuploidy in aging women.
- This could suggest that the use of high doses of exogenous hormones for ovarian stimulation in older patients perturbs the process of meiosis.

- Miscarriage risk and the prevalence of aneuploid oocytes are relatively low and change little until approximately age 35, and then increase progressively, reaching 70% at age 40 and virtually 100% after age 45.
- **evidence strongly suggests that the primary cause of the age dependent decrease in fecundability and increase in the incidence of miscarriage is**

an increasing prevalence of aneuploidy in aging oocytes resulting at least in part from disordered regulatory mechanisms governing meiotic spindle formation and function.

Aging and the Uterus

- Aging does not appear to have any significant adverse effect on the uterus.
- **Live birth rates in donor egg IVF cycles relate to the age of the donor, not the age of the recipient.**

Aging and Male Fertility

- Overall, the available evidence suggests a **negative correlation** between **male age** and **pregnancy rates**. The **time to conception increases** with male age.
- However, because there is **little or no overall measurable decline** in **male fertility before age 45-50**, male factors generally contribute relatively little to the overall age-related decline in fertility.

Ovarian Reserve and Its Assessment

- It is important to emphasize that such tests **cannot** and do not **establish a diagnosis of DOR**; they only **identify women more likely to exhibit a poor response to gonadotropin.**

Basal FSH and Estradiol Concentrations

- Serum FSH concentration was one of the earliest and commonly used tests of ovarian reserve.
- serum FSH concentration is best obtained during the early follicular phase (cycle days 2–4).
- **With current assays, FSH levels greater than 10 IU/L (10–20 IU/L) have high specificity (80–100%) for predicting poor response to stimulation.**

- **The basal serum estradiol concentration, by itself, has little value as an ovarian reserve test, but can provide additional information that helps in the interpretation of the basal FSH level.**
- An early elevation in serum estradiol reflects advanced follicular development and early selection of a dominant follicle (as classically observed in women with advanced reproductive aging) and will suppress FSH concentrations, thereby possibly masking an otherwise obviously high FSH level indicating DOR.

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

- When both FSH and estradiol are elevated, ovarian response to stimulation is likely to be very poor.
- Due to their low diagnostic performance, basal FSH and estradiol measurements are being increasingly replaced with serum AMH and AFC in daily practice.

Clomiphene Citrate Challenge Test

- The CCCT is a provocative and possibly more sensitive test of ovarian reserve that probes the endocrine dynamics of the cycle under both basal and stimulated conditions, before (cycle day 3 FSH and estradiol) and after (cycle day 10 FSH) treatment with clomiphene citrate (100 mg/day, cycle days 5–9). The smaller follicular cohorts in aging women produce less inhibin B and estradiol, resulting in less negative feedback inhibition on clomiphene-induced pituitary FSH release, causing an exaggerated increase in FSH concentrations.

Inhibin B

- Inhibin B is secreted primarily during the follicular phase by the granulosa cells of smaller antral follicles. **inhibin B is generally not regarded as a reliable measure of ovarian reserve.**

Antimüllerian Hormone

- Antimüllerian hormone (AMH) is produced by the granulosa cells of preantral and small antral follicles, beginning when primordial follicles start developing into primary follicles and ending when early antral follicles reach a diameter of 2–6 mm.

The number of small antral follicles correlates with the size of the residual follicular pool and AMH.

- levels decline progressively, becoming undetectable near the menopause. **Because AMH derives from preantral and small antral follicles, levels were thought to be gonadotropin-independent and exhibit little variation within and between cycles.** However, recent studies suggest AMH levels decrease with the use of oral contraceptives and GnRH agonists.

- AMH is a very promising screening test for DOR but is likely to be more useful in a general IVF population or in women at high risk for DOR than in women at low risk for DOR.
- Low threshold values have good specificity for poor response to ovarian stimulation, but not for predicting pregnancy.

Antral Follicle Count

- Antral follicles are FSH sensitive and can progress to more advanced stages of development when stimulated with exogenous FSH.
- **Histologic studies have revealed that the number of small antral follicles in the ovaries is proportional to the number of primordial follicles remaining.**
- **Therefore, as the supply of primordial follicles decreases, the number of visible small antral follicles also declines.**

- The antral follicle count (AFC; total number of antral follicles measuring 2–10 mm in both ovaries) thus provides an indirect but useful measure of ovarian reserve.

- Some, perhaps as much as half, of the antral follicles that can be imaged are probably in the process of atresia, but there is no way other than observing their response to FSH stimulation to distinguish them from viable growing follicles.
- However, AFC correlates well with oocyte yield in IVF cycles, suggesting that gonadotropin stimulation can still rescue follicles that may be in the early stages of atresia.

- an AFC threshold value of three to four follicles has high specificity (73–100%) for predicting poor response to ovarian stimulation and failure to conceive.
- **A low AFC has high specificity for predicting poor response to ovarian stimulation and treatment failure, making it a useful test, but low**

  sensitivity limits its overall clinical utility.

Ovarian Volume

- Overall, ovarian volume has very limited clinical utility as an ovarian reserve test.
- The best overall strategy would seem to limit ovarian reserve testing to women at increased risk for having a diminished ovarian reserve and to apply highly specific threshold values to minimize the risk for a false-positive result.
- Age over 35, Unexplained infertility ,to identify unsuspected loss of ovarian reserve Family history of early menopause, Previous ovarian surgery (ovarian cystectomy or drilling, unilateral oophorectomy), chemotherapy, or radiation Smoking Demonstrated poor response to exogenous gonadotropin stimulation.

- Ovarian reserve tests always should be interpreted with caution.
- An abnormal test result does not preclude the possibility of pregnancy. Except perhaps when grossly abnormal, test results should not be used to deny treatment, but only to obtain prognostic information that may help to guide the choice of treatment and best use of available resources.
- Although the probability of pregnancy may be low, many with abnormal test results will achieve pregnancy if afforded the chance.

GUIDING PRINCIPLES FOR EVALUATION AND TREATMENT OF INFERTILITY

- From the beginning, the evaluation of infertility should focus on the couple and not on one or the other partner.

Lifestyle and Environmental Factors

- In women, obesity is associated with menstrual dysfunction, decreased fertility, and increased risks of miscarriage and obstetric and neonatal complications.
- In men, obesity is associated with abnormal semen parameters and can adversely affect fertility.
- Substance abuse :Marijuana , Cocaine, Heavy alcohol consumption , caffeine ingestion >200 mg daily , smoking
- Per chlorethylene in the dry-cleaning industry, toluene in the printing business, ethylene oxide
- Environmental exposure to herbicides or fungicides has been associated with decreased fertility

- For couples attempting to conceive, there is fair evidence to support recommendations for smoking cessation and efforts to achieve a BMI between 20 and 25 kg/m2 . Recommendations to limit alcohol consumption to four or fewer drinks per week and to limit caffeine intake to less than 200 mg/day also are reasonable and consistent with available evidence. However, there have been no randomized controlled trials demonstrating that such lifestyle modifications improve fertility.

Normal Reproductive Efficiency

- In normally fertile couples, cycle fecundity averages 20%and does not exceed approximately 35% even when coitus is carefully timed.

Months of Exposure	% Pregnant
3 mo	57%
6 mo	72%
1 y	85%
2 y	93%

- A normal sperm can survive in the female reproductive tract and retain the ability to fertilize an egg for at least 3 and up to 5 days, but an oocyte can be fertilized successfully for only approximately 12-24 hours after ovulation. Consequently, virtually all pregnancies result from intercourse occurring sometime within the 6- day interval ending on the day of ovulation.

- ” For most couples, the simple recommendation for intercourse approximately once every 2–3 days can avoid an unnecessary source of stress while also helping to ensure that coitus occurs during the interval of highest fertility.

Causes of Infertility

- The major causes of infertility include ovulatory dysfunction (20–40%),
- tubal and peritoneal pathology (30–40%),
- and male factors (30–40%); uterine pathology is relatively uncommon, and the remainder is largely unexplained.
- Many couples suffer from multiple etiologies.

Key Points: Human Reproductive Process

- Sperm must be deposited at or near the cervix at or near the time of ovulation, ascend into the fallopian tubes, and have the capacity to fertilize the oocyte (male factor).
- Ovulation of a mature oocyte must occur, ideally on a regular and predictable basis (ovarian factor).
- The fallopian tubes must capture ovulated ova and effectively transport sperm and embryos (tubal factor).
- The uterus must be receptive to embryo implantation and capable of supporting subsequent normal growth and development (uterine factor).

- IVF can effectively bypass irreparable tubal occlusive disease, and intracytoplasmic sperm injection (ICSI) can overcome even severe abnormalities of semen quality.
- In women with POF, women beyond normal reproductive age, and women without ovaries, IVF using donor oocytes is highly successful.

Indications for Evaluation

- **The probability for achieving a live birth without treatment decreases with increasing age and duration of infertility.**
- **The largest majority of spontaneous pregnancies occur within 3 years; thereafter, the prognosis for success without treatment is relatively poor.**
- Predictably, the diagnoses of anovulation and unexplained infertility have the best prognosis.

- 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 in the presence of obvious risk factors, such as irregular or infrequent menses, history of pelvic infection, surgery or endometriosis, or having a male partner with known or suspected poor semen quality, and also is warranted after 6 months of unsuccessful effort for women over the age of 35 years.

PRELIMINARY EVALUATION OF THE INFERTILE COUPLE

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.

- Irregular or infrequent menses indicate ovulatory dysfunction. Previous treatment for cervical intraepithelial neoplasia or observation of a mucopurulent cervicitis or cervical stenosis helps to identify unusual women in whom the cervix may present an obstacle.
- A history of previous hysteroscopic or reconstructive uterine surgery or recently developing symptoms of menorrhagia suggest an abnormality of the uterine cavity.
- Worsening dysmenorrhea, new onset of dyspareunia, or physical findings of focal tenderness or cul-de-sac nodularity suggest endometriosis.
- A history of pelvic infection, septic abortion, ruptured appendix, ectopic pregnancy, abdominal myomectomy, or adnexal surgery should raise suspicion for tubal or peritoneal disease.

Screening Tests

- **Cervical cancer**
- blood type, Rh factor
- carrier screening for cystic fibrosis and spinal muscular atrophy,
- complete blood count
- thalassemias and hemoglobinopathies
- family history of fragile X- related disorders or intellectual disability suggestive of fragile X syndrome or women with premature ovarian insufficiency should be offered fragile X permutation carrier screening

- When a woman is found to be a carrier for a specific condition, her reproductive partner should be offered screening to provide accurate genetic counseling regarding risk of an affected child if he tests positive and reproductive options (e.g., donor gametes, preimplantation genetic diagnosis, prenatal diagnosis).
- undocumented previous rubella infection or vaccination should be tested for immunity and vaccinated if seronegativ.
- women without history of previous infection or evidence of immunity or vaccination against varicella (chicken pox) receive two doses of vaccine and avoid pregnancy for 1 month after each dose.
- **sexually transmitted infections**

MALE FACTOR: ABNORMALITIES OF SEMEN QUALITY

- male factors explain or contribute significantly to infertility in up to 35% of couples.
- Invasive diagnostic procedures, including hysterosalpingography (HSG), in the female partner generally can be deferred until evaluation of the male is completed.

OVARIAN FACTOR: OVULATORY DYSFUNCTION

- Overall, disorders of ovulation account for approximately 15% of the problems identified in infertile couples.
- **Menstrual History :Women with regular menses are almost always ovulatory.**
- **Women with irregular or infrequent menses may ovulate, but not consistently, and do not require specific diagnostic tests to prove what is already obvious.**

Basal Body Temperature

- Synthetic progestins commonly used to induce menses in amenorrheic women (medroxyprogesterone acetate, norethindrone acetate) have similar thermogenic properties and also raise BBT.
- The ideal BBT recording is distinctly biphasic and reveals a cycle between 25 and 35 days in length, with menses beginning 12 days or more after the rise in temperature.
- The shift in BBT occurs when progesterone concentrations rise above approximately 3– 5 ng/mL, 1–5 days after the midcycle LH surge and up to 4 days after ovulation

- **In cycles monitored with BBT, the interval of highest fertility spans the 7-day interval immediately before the midcycle rise in BBT.**
- **Coital timing can be optimized by suggesting intercourse on alternate days beginning 7 days before the earliest observed rise in BBT and ending on the latest day it has been observed.**
- Since BBT cannot reliably define the time of ovulation and can become tedious, it is not the method of choice for evaluating ovulatory function for most infertile women

Serum Progesterone Concentration

- **A serum progesterone measurement is the simplest, most common, objective, and reliable test of ovulatory function, as long as it is appropriately timed.**
- Progesterone levels generally remain below 1 ng/mL during the follicular phase, rise slightly on the day of the LH surge (1–2 ng/mL) and steadily thereafter, peak 7–8 days after ovulation, and decline again over the days preceding menses.

- A progesterone concentration less than 3 ng/mL implies anovulation, except when drawn immediately after ovulation or just before the onset of menses, when lower levels naturally might be expected.

- Ideally, the serum progesterone level should be drawn approximately 1 week before the expected onset of menses, when the concentration is at or near its peak. Contrary to popular belief and practice, cycle day 21 is not always the best time to measure the serum progesterone concentration.

Urinary LH Excretion

- The midcycle LH surge is a relatively brief event, typically lasting between 48 and 50 hours from start to finish.
- LH has a short half-life and is rapidly cleared via the urine. In most cycles, the test is positive on a single day, occasionally on 2 consecutive days. results correlate best with the serum LH peak when testing is performed in the late afternoon or early evening hours (4:00–10:00 P.M.),

- Ovulation generally occurs 14-26 hours after detection of the LH surge and almost always within 48 hours.
- Consequently, the interval of greatest fertility includes the day the surge is detected and the following 2 days.
- The day after the first positive test generally is the one best day for timed intercourse or insemination.

Endometrial Biopsy and Luteal Phase Deficiency

- **In the absence of treatment with exogenous progesterone or a synthetic progestin, a secretory endometrium implies recent ovulation.**
- For women with chronic anovulation of long duration, biopsy can identify or exclude endometrial hyperplasia that requires specific treatment.
- In those few individuals suspected of harboring a chronic endometritis, biopsy is diagnostic.

In the past, endometrial biopsy for diagnosis of luteal phase deficiency was considered a basic element of the infertility evaluation, but no longer.

Inadequate corpus luteum progesterone production or "luteal phase deficiency" (LPD) was long considered an important cause of both infertility and early pregnancy loss.

- In theory, because the human implantation window is relatively narrow (spanning the interval from approximately 6 to 10 days after ovulation), low circulating progesterone levels could be expected to result in delayed endometrial maturation, causing a shift in the implantation window and failed or late implantation. A long delay would threaten embryo viability or prevent implantation.

Transvaginal Ultrasonography

- preovulatory follicle grows at a predictable pace, approximately 2 mm per day (range: 1–3 mm/day). After ovulation, the follicle collapses, margins become less distinct, the density of internal echoes increases, and the volume of cul-de-sac fluid increases.
- The follicle may grow at an abnormal pace, collapse when still relatively small, or continue to grow but fail to rupture and persist as a cyst for days after the LH surge—the luteinized unruptured follicle.

- **Because treatment with prostaglandin synthase inhibitors (NSAIDs) can disrupt the ovulatory process and predispose to a luteinized unruptured follicle, their use is best limited to the menstrual phase of the cycle in women attempting to conceive.**

Summary: Assessment of Ovulation

- In women with oligomenorrhea or amenorrhea, no formal evaluation is needed to establish a diagnosis of ovulatory dysfunction, but endometrial biopsy to exclude hyperplasia may be prudent, depending on duration.
- When the only objective is to confirm ovulatory function, as in those with regular monthly menses, a properly timed serum progesterone concentration is the simplest and most reliable method.

CERVICAL FACTOR: ABNORMALITIES OF SPERM-MUCUS INTERACTION

- Estrogen stimulates cervical mucus production, and as levels rise during the follicular phase, mucus becomes more abundant and watery, less cellular, and more easily penetrated by sperm.
- Progesterone inhibits cervical mucus production and renders it opaque, viscid, and impenetrable. **The postcoital test for diagnosis of cervical factor is no longer recommended.**

UTERINE FACTOR: ANATOMIC AND FUNCTIONAL ABNORMALITIES

- The anatomic uterine abnormalities that can adversely affect fertility include congenital malformations, leiomyomas, and intrauterine adhesions; endometrial polyps also have been implicated, but their reproductive implications are less clear.

The only functional uterine abnormality of specific interest in the evaluation of infertility is chronic endometritis.

Whereas abnormalities of endometrial receptivity (including LPD) might be viewed as another.

- There are three basic methods for evaluation of the uterine cavity: HSG, TVUS or saline sonohysterography, and hysteroscopy.
- HSG is the traditional method and most often still the best initial test because it also evaluates tubal patency.
- However, in women with no risk factors for tubal disease and those whose tubal status is already known (from earlier surgery for other indications) or is largely irrelevant (as in women who require IVF for severe male factor infertility), ultrasonography offers a simpler and better tolerated alternative that also may reveal unsuspected ovarian pathology (cyst, endometrioma), with no radiation exposure.

Hysterosalpingography

- HSG accurately defines the size and shape of the uterine cavity, provides clear images of most uterine developmental anomalies (unicornuate, septate, bicornuate, and didelphys), and, with exceptions, also identifies submucous myomas and intrauterine adhesions that can have important reproductive implications.
- Although HSG also may reveal endometrial polyps, sonohysterography is a more sensitive method for their detection. A slow injection of contrast medium helps to minimize the risk that a cavitary lesion will be obscured and go undetected.

Transvaginal Ultrasonography and Saline Sonohysterography

- TVUS is another method for evaluation of uterine factors in infertile women. Saline sonohysterography, involving TVUS during or after introduction of sterile saline through a catheter designed for the purpose, crisply defines cavity contours and readily demonstrates even small, but potentially important, intrauterine lesions.

- Three-dimensional (3D) ultrasonography has the advantage of obtaining a coronal view and providing accurate and reproducible information about external and internal contours of the uterus, ideally when the endometrium is 5 mm or thicker. Three-dimensional ultrasonography showed 100% specificity and

sensitivity for diagnosing congenital uterine anomalies in two studies, and its concordance with specificity and sensitivity of laparoscopy and hysteroscopy was reported to be 100% and 96%, respectively.

- MRI may produce more accurate results than 3D ultrasonography (USG) in some extreme cases. Accuracy for diagnosing fibroids dropped from 98% to 89% for 3D ultrasonography and from 100% to 94% for MRI, when five or more fibroids were present.

Hysteroscopy

- Hysteroscopy is the gold standard method for both diagnosis and treatment of intrauterine pathology that may adversely affect fertility.

Congenital Uterine Anomalies

- **Developmental uterine anomalies have long been associated with pregnancy loss and obstetric complications, but affected women generally are not infertile.**
- Septate uterus is the anomaly most highly associated with reproductive failure and obstetrical complications, including first- and second-trimester miscarriage, preterm delivery, fetal malpresentation, intrauterine growth restriction, and infertility.
- The mechanisms responsible are poorly understood, but poor septal blood supply, resulting in poor implantation efficiency and embryo growth, and cervical incompetence are the usual suspects.

- Today, hysteroscopic septum resection is a relatively straightforward and brief outpatient procedure associated with low morbidity, no risk of adnexal adhesions or obligation to cesarean delivery, and a prompt and uneventful Recovery.
- surgical correction of a septate uterus, especially in women over age 35, women with infertility of long duration, women with other indications for surgical treatment, and women who require IVF or other treatments associated with increased risk of multifetal gestation and pregnancy loss.

Uterine Myomas

- Infertility relating to myomas has been attributed to all of the following

  Mechanisms:

- Displacement of the cervix, decreasing exposure to sperm
- Enlargement or deformity of the uterine cavity, interfering with sperm

  transport

- Obstruction of the interstitial segment of the fallopian tubes

- **Distorted adnexal anatomy, interfering with ovum capture**
- **Distortion of the uterine cavity or increased or abnormal myometrial**

  contractions, inhibiting sperm or embryo transport
- **Impaired uterine blood flow, chronic endometritis, or decreased endometrial receptivity, interfering with implantation**
- There is a clear consensus that submucous myomas have significant adverse effect on clinical pregnancy rates (OR = 0.3, CI = 0.1–0.7) and delivery rates Available data also support the conclusion that submucous myomas increase risk for miscarriage by more than threefold, All of the evidence concerning the effects of subserosal myomas is consistent in finding no evidence of adverse effects on IVF outcomes.

- evidence indicates that submucous myomas reduce IVF success rates by approximately 70% and intramural myomas by approximately 20-40%, and subserosal myomas have no adverse impact on outcomes.
- Submucous myomas increase risk for miscarriage after successful IVF at least threefold and intramural myomas by more than half.

Intrauterine Adhesions (Asherman Syndrome)

- Intrauterine adhesions develop as a result of trauma. Any insult severe enough to remove or destroy the endometrium can cause adhesions.
- The gravid uterus is particularly susceptible to injury, especially between the second and fourth weeks postpartum. Inflammation or infection also may predispose to adhesions.
- In approximately 90% of cases, intrauterine adhesions relate to curettage for pregnancy complications, such as missed or incomplete abortion or retained products of conception.

- Adhesions also can develop after abdominal or hysteroscopic myomectomy, septum resection, or other uterine surgery. genital tuberculosis is an important cause of intrauterine adhesions.
- Intrauterine adhesions can be asymptomatic or cause menstrual disorders (hypomenorrhea, amenorrhea, dysmenorrhea), pain, recurrent miscarriage, or

Infertility When suspected, HSG and saline sonohysterography confirm the presence of intrauterine adhesions.

- Postoperative treatment with exogenous estrogens to promote rapid re-epithelialization and reduce risks of recurrent adhesions is frequently used, but its efficacy has not been established; a typical regimen involves treatment with 2–6-mg estradiol daily for 4 weeks, adding a progestin (e.g., medroxyprogesterone acetate 10 mg daily) during the last week.
- Surgical results should be evaluated by HSG or saline sonohysterography after

  menses.

Endometrial Polyps

- Endometrial polyps are hyperplasic endometrial growths with a vascular center and a sessile or pedunculated shape extending into the uterine cavity. They are generally rare in young women and increase in incidence with age. Saline sonohysterography is the most useful method of imaging for d etection of endometrial polyps
- Overall, hysteroscopic polypectomy results in a greater than twofold increase in clinical pregnancy among subfertile or infertile women who subsequently undergo IUI.

Chronic Endometritis

- Available evidence suggests that chronic subclinical endometritis is relatively common in women with symptomatic lower genital tract infections, including cervicitis and recurrent bacterial vaginosis.
- Mucopurulent cervicitis is highly associated with chlamydia (Chlamydia trachomatis) and mycoplasma (Mycoplasma genitalium) infection, and both organisms, in turn, are associated with chronic endometritis, which likely plays a role in the pathogenesis of tubal factor infertility. While some retrospective studies suggest that up to 57–66% of women with unexplained infertility or unexplained recurrent implantation failure are diagnosed with chronic endometritis.

TUBAL FACTOR: TUBAL OCCLUSION AND ADNEXAL ADHESIONS

- **A history of pelvic inflammatory disease (PID), septic abortion, ruptured appendix, tubal surgery, or ectopic pregnancy strongly suggests the possibility of tubal damage.** Many such women will have detectable chlamydia antibodies suggesting prior infection HSG and laparoscopy are the two classic methods for evaluation of tubal patency in infertile women.

Hysterosalpingography

- HSG is best scheduled during the 2–5-day interval immediately following the end of menses, to minimize the risk for infection, to avoid interference from intrauterine blood and clot, and to prevent any possibility that the procedure might be performed after conception.

Treatment with antibiotics (doxycycline 100 mg twice daily for 5 days, beginning 1–2 days before HSG) is prudent when tubal disease is highly suspected, and specifically indicated when HSG reveals distal tubal obstruction, because risk for acute salpingitis is increased (approximately 10%) and treatment can prevent clinical infection.

- To minimize the risk of infection, HSG is best avoided altogether for at least several weeks following any episode of acute PID.

- **The clinical implications are that when HSG reveals obstruction, there is still a relatively high probability (approximately 60%) that the tube is open, but when HSG demonstrates patency, there is little chance the tube is actually occluded (approximately 5%).**

Laparoscopy

- Laparoscopy is regarded generally as the definitive test for the evaluation of tubal factors. Injection of a dilute blue dye through a cannula attached to the cervix or an intrauterine manipulator permits evaluation of tubal patency (“chromotubation”).

Chlamydia Antibody Tests

- **In summary, chlamydia antibody tests can provide useful information, but also have pitfalls that limit their clinical utility. Currently, diagnostic performance of chlamydia antibody testing is limited, and HSG or other**

imaging modalities remain the standard for assessment of tubal patency

- it might be effective if limited to women with unexplained infertility (including a normal HSG).

Tubal Surgery in the Era of ART

- The decision between surgery and IVF should be based on the following:
- The age of woman
- Ovarian reserve
- Prior fertility status
- Number of children desired
- Site and extent of tubal damage
- Presence or absence of other factors necessitating IVF
- Surgeon's experience
- Success rate of IVF program
- Patient preference, that is, religious belief, cost, and insurance coverage for

- **each optionYounger women**, women with normal/high ovarian reserve, proven fertility, desiring multiple children will comprise more appropriate candidates for surgical repair.
- A semen analysis of the male partner should precede the decision.
- A preoperative HSG can be useful to assess the proximal segments and to confirm the type of sterilization performed.
- **The most important prognostic factor for achieving a live birth after microsurgical sterilization reversal is age. The type and location of procedure and the final length of the repaired fallopian tubes are also thought to play a role.**

- Younger women, those whose sterilization was performed using rings and clips, and women having no other infertility factors have the best prognosis; success rates are lower for older women, those who were sterilized by cautery (particularly multipleburn techniques), and women with other infertility factors.
- **In properly selected candidates, overall conception rates are generally quite good (45-82%) after microsurgical sterilization reversal.** Risk for ectopic pregnancy ranges between 2% and 10% and is higher after isthmic-ampullary than after isthmic-isthmic Anastomoses.
- **The best candidates for the procedure are young women desiring more than one additional pregnancy and having no other infertility factors.**

Distal Tubal Obstruction

- In younger women with mild distal tubal occlusive disease, laparoscopic surgery may be viewed as an alternative to IVF, but when disease is severe or pregnancy does not occur during the first postoperative year, IVF is the logical choice.
- For older women with any significant degree of distal tubal disease, IVF is generally the first and best option because cycle fecundability after distal tubal surgery is low (1–2%), time is limited, and IVF is both more efficient and more effective. laparoscopic salpingectomy or tubal occlusion improves IVF pregnancy rates in women with hydrosalpinges.

Proximal Tubal Obstruction

- Proximal tubal occlusions represent 10–25% of all tubal obstructions observed with HSG, many of which are not real (20–40%). Mucus plugs, cellular debris, or uterotubal spasm can cause pseudo proximal obstruction.
- Repeated HSG can decrease the number of false-positive tests of tubal patency.
- pathogenesis of proximal tubal occlusive disease:
- salpingitis isthmica nodosa (SIN), chronic inflammation, and intratubal endometriosis.

UNEXPLAINED INFERTILITY

- **At a minimum, the diagnosis of unexplained infertility implies normal semen analysis, ovulatory function, a normal uterine cavity, and at least unilateral tubal patency.**
- Undoubtedly, much of unexplained infertility relates to the natural decline in fertility with increasing age. Unexplained infertility is more common in women over age 35.

- In studies evaluating treatments for unexplained infertility,

untreated patients have a cycle fecundability ranging typically between 2% and 4%, or about 80-90% lower than in normal fertile couples (20-25%).

- The likelihood of pregnancy without treatment decreases progressively with increasing age of the female partner and increasing duration of infertility.

TREATMENT

- Ovarian Stimulation

- Ovulation induction is indicated in women with anovulation or oligoovulation. However, any identified condition associated with ovulatory disorders should be addressed before initiating ovulation induction therapy. Such conditions include thyroid disorders, hyperprolactinemia, PCOS, and high levels of stress (including psychological stress, intense exercise, and eating disorders) causing hypothalamic dysfunction.

Clomiphene

- **The best available evidence suggests that treatment with IUI in natural cycles has no clinically important effects.**
- The most commonly used medication for ovulation induction is clomiphene citrate. However, letrozole, an aromatase inhibitor, should be considered as an alternative first-line therapy.
- The antiestrogen effects of clomiphene induce gonadotropin release from the pituitary, which stimulates follicle development in the ovaries . .starting between cycle days 3 and 5. Transvaginal ultrasound performed on cycle day 11 or 12 may identify a developing follicle. When ultrasound is used and a mature follicle is identified (average diameter > 18 mm), ovulation can be triggered by administering a subcutaneous injection of hCG.

- The exogenous hCG effectively simulates the LH surge and ovulation occurs; this practice enables the proper timing of intercourse or insemination.
- The use of clomiphene is associated with a 10% risk of multiple gestations, the majority of which are twin gestations, and a small risk of ovarian hyperstimulation and cyst formation.
- Aromatase inhibitors, compared to clomiphene, in recent trials are associated with an increased ovulation rate and increased live-birth rate in patients with PCOS.

Controlled Ovarian Hyperstimulation and IUI

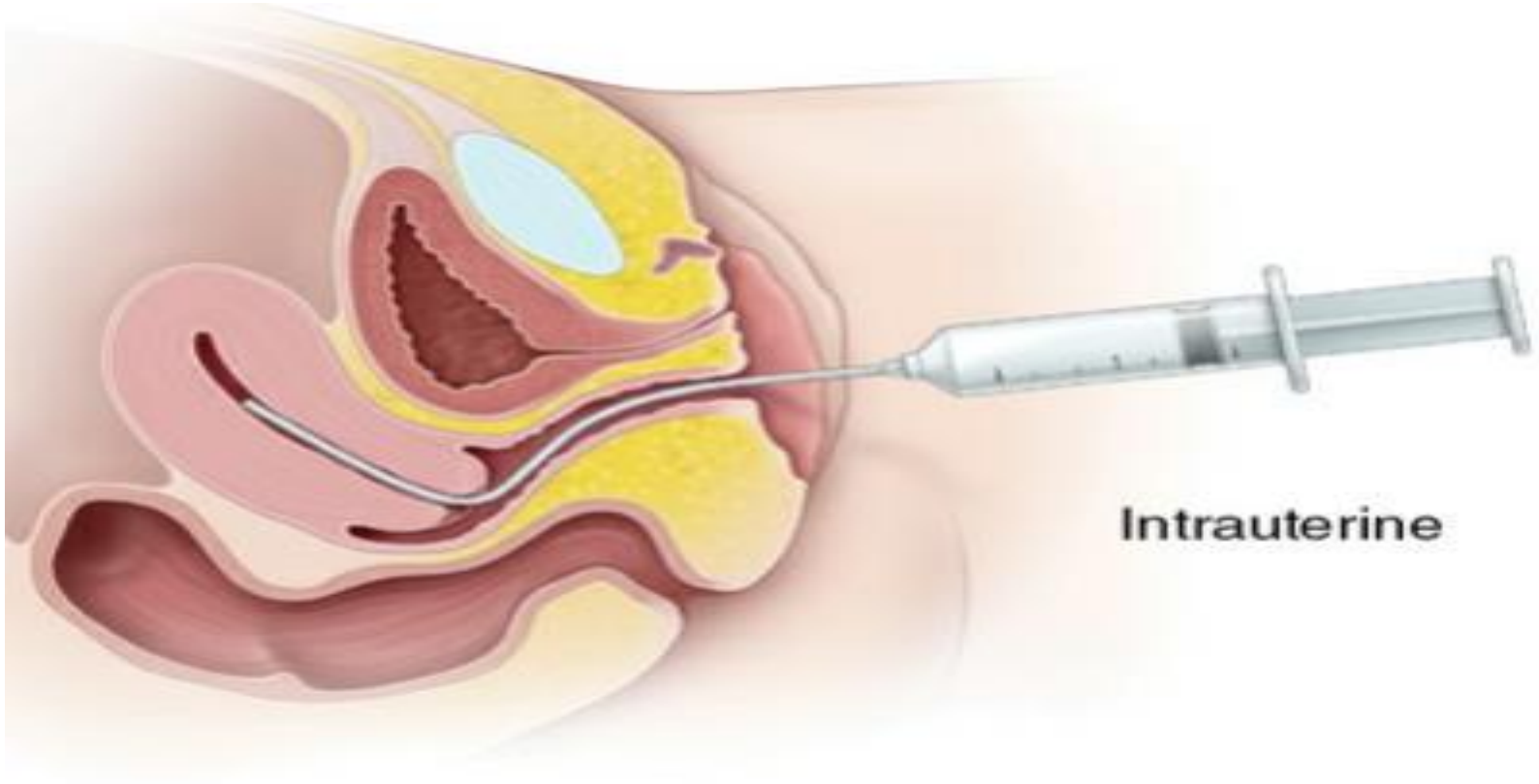
- The use of gonadotropins is commonly referred to as controlled ovarian hyperstimulation (COH). This therapy aims to achieve monofollicular ovulation in anovulatory women (particularly those who do not respond to clomiphene) and ovulation of several mature follicles in other infertile women.
- When at least one mature follicle is identified (average follicle diameter of 18 mm and serum estradiol concentration >200 pg/mL), hCG is administered to trigger ovulation. Timed inseminations are commonly performed within 12 to 36 hours from hCG administration.
- The risks of this therapy include ovarian hyperstimulation syndrome, which can require intensive therapy, a 25% incidence of multiple gestations, and an increased risk of ectopic pregnancy.

Intrauterine Insemination

- Before performing IUI, an ejaculated semen specimen is washed to remove prostaglandins, bacteria, and proteins.
- A total motile sperm count (concentration multiplied by motility) of at least 1 million must be present, as pregnancy is rarely achieved with lower counts. In couples with infertility, and particularly in those with mild male infertility, pregnancy rates are increased with IUI.

- In summary, treatment with **gonadotropins and IUI** is modestly **effective treatment** for couples with longer **durations of unexplained infertility (>3 years)** and should be considered for couples who **fail to conceive during treatment with clomiphene and IUI** and when clomiphene treatment fails to stimulate multiple follicular development, especially when IVF is not a viable option.

Based on the results of the two large randomized trials mentioned above, gonadotropins and IUI could also be utilized as the first alternative; however, the concerns regarding **multiple pregnancy** often preclude this approach.



. Intrauterine insemination technique.

Assisted Reproductive Technology

- In summary, **IVF is clearly the most effective treatment** for couples with

  unexplained infertility, regardless whether it is the first or the last treatment.

ADOPTION

- With proper evaluation and treatment, the majority of couples evaluated for infertility will achieve pregnancy. For those who fail treatments, ART with donor eggs and/or a gestational surrogate and adoption are realistic options.

Thanks for your attention