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Overview of Female Infertility: Causes, Evaluation, And Management

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Abstract | **Review Article**

Introduction: Infertility is a disease of the male or female reproductive system defined by the failure to achieve a pregnancy after 12 months or more of regular unprotected sexual intercourse. In the female reproductive system, infertility may be caused by a range of abnormalities of the ovaries, uterus, fallopian tubes, and the endocrine system, among others. Infertility can be primary or secondary. Primary infertility is when a pregnancy has never been achieved by a person, and secondary infertility is when at least one prior pregnancy has been achieved. ***Objectives:*** Describe the epidemiology of female infertility. Review the most common findings of female infertility. Outline the management for known causes of female infertility. Explain the importance of improving health care coordination among the interprofessional team to enhance and improve outcomes for female infertility patients.

Keywords: "infertility", "uterus", "ultrasound scan", "transvaginal sonography", "endometrial polyp", "fibroma", "leiomyoma", "endometrial hyperplasia", "intrau-terine adhesions", "Asherman's syndrome", "adenomyosis", "congenital uterine anomalies", "congenital uterine malformations".

Etiology

In 37% of infertile couples, female infertility was the cause;

In 35% of couples, both male and female causes were identified;

In 8%, there was male factor infertility

The most common identifiable factors of female infertility are as follows:

- Ovulatory disorders - 25%
- Endometriosis - 15%
- Pelvic adhesions - 12%
- Tubal blockage - 11%
- Other tubal/uterine abnormalities - 11%
- Hyperprolactinemia - 7%

Epidemiology

Infertility rates are higher in Eastern Europe, North Africa, and the Middle East. Worldwide, 2% of women aged 20 to 44 were never able to have a live birth, 11% with a previous live birth were unable to have an additional birth.

Risk Factors for Female Infertility Include

- Age: As a woman gets older, her chances of infertility increases. In women aged 15 to 34 years, infertility rates ranged from 7.3 to 9.1%. In women ages 35 to 39 years old, the infertility rates increased to 25%. In women from ages 40 to 44 years, the infertility rates increased to 30%
- Weight. Extreme weight levels, either high or low, can contribute to infertility.
- Smoking. Cigarette smoking can impair a woman's fertility.
- Alcohol. More than 2 drinks a day may impair a woman's fertility.
- Hormone issue that prevents ovulation.
- Abnormal menstrual cycle.
- Endometriosis.
- Structural problems (problems with the fallopian tubes, uterus or ovaries).
- Uterine fibroids.
- Cysts.
- Tumors.
- Autoimmune disorders (lupus, rheumatoid arthritis, Hashimoto's disease, thyroid gland conditions).
- Sexually transmitted infections (STIs).
- Polycystic Ovary Syndrome (PCOS).
- Primary Ovary Insufficiency (POI).
- DES syndrome (DES is a medication that was given to women to prevent complications in pregnancy like premature birth or miscarriage.

However, this medication has caused infertility in some of the children of mothers who took DES.).

- A past ectopic (tubal) pregnancy.

Pathophysiology

Anovulation

World Health Organization subdivided ovulatory disorders into four classes:

1. Hypogonadotropic hypogonadal anovulation: i.e., hypothalamic amenorrhea
2. Normo-gonadotropic normo-estrogenic anovulation: i.e., polycystic ovarian syndrome (PCOS)
3. Hypergonadotropic hypoestrogenic anovulation: i.e., premature ovarian failure
4. Hyperprolactinemic anovulation: i.e., pituitary adenoma

Endometriosis

Endometriosis is most commonly found in the pelvis but can spread throughout the entire abdomen and affects 10% to 15% of reproductive-age women. Of women with endometriosis, 40% to 50% will experience infertility.

Endometriosis is categorized into four stages, according to the American Society of Reproductive Medicine, with stage I being minimal and stage IV severe.

Endometriosis is known to cause infertility, but the pathophysiology is thought to change according to the stage.:

- For stages I and II: infertility is believed to be associated with inflammation with increased production of prostaglandins and cytokines, macrophages, and natural killer cells.
- The inflammation impairs ovarian and tubal function resulting in defective follicular formation, fertilization, and implantation.
- Stages III and IV are associated with pelvic adhesions and/or masses that distort pelvic anatomy; this will inherently impair tubal motility, oocyte release, and sperm motility.
- Also, advanced endometriosis is hypothesized to impair folliculogenesis, which reduces the fertilization potential.

Pelvic/Tubal Adhesions

Infectious processes within the abdomen are the leading cause of pelvic/tubal adhesions; the most common infectious process to affect infertility is pelvic inflammatory disease (PID). The microorganism that carries the greatest risk of infertility in association with PID is Chlamydia trachomatis. One in 4 women with tubal factor infertility will have positive antibodies to chlamydia, which are inversely proportional to pregnancy rates. The number of PID episodes and the severity play a role in the likelihood of infertility. One study demonstrated that the pregnancy rates following PID were 89% after 1 episode, 77% after two episodes, and 46% after three episodes. In terms of PID severity of mild, moderate, and severe, the livebirths rates were 90%, 82%, and 57%, respectively.

Tuberculosis is a common cause of distal tubal occlusion for women from Northern India and Nepal. In areas with a high prevalence of tuberculosis, evaluation of the female partner for tuberculosis using a polymerase chain reaction test on an endometrial biopsy specimen identified women who would benefit from antimicrobial therapy.

Hydrosalpinges, are a tubal abnormality caused by acute and chronic inflammation that damages the structural integrity of the fallopian. This damage leads to tubal obstruction, which blocks the distribution of physiologic fluid in the fallopian tube and results in fluid accumulation. The belief is that hydrosalpinges impair fertility through the retrograde flow of toxins and prostaglandins into the endometrium, creating a hostile environment for implantation by impairing endometrial receptivity. The literature has demonstrated that patients undergoing in-vitro fertilization have a 50% decrease in pregnancy if a hydrosalpinx is present.

A history of a ruptured appendix increases the risk of developing tubal factor infertility. In one case-control study, a history of ruptured appendix was associated with a 4-8-fold increase in the risk of tubal infertility. Appendicitis without rupture was not associated with an increased risk of tubal infertility.

Uterine Causes

Cervical Factor Infertility

The cervix is an active participant in shepherding sperm from the vagina to the upper reproductive tract. In the normal cervix, the secreted cervical mucus has physicochemical properties that facilitate the transport of sperm. Congenital malformation and trauma to the cervix may impair the ability of the cervix to produce normal mucus.

Historically the postcoital test was used to assess sperm interaction with the cervical mucus, but it is rarely performed in modern fertility practice. There is little consensus on how to interpret the test. Some authorities suggest that a normal test requires more than 20 sperm per high-power field. Other authorities conclude that the presence of a single sperm indicates a normal test. The link between the results of a postcoital test and fertility potential is tenuous. In one study of the relationship between the postcoital test and fecundability, 20% of fertile women were observed to have one sperm or less per high-power field. In another study, fecundability did not seem to be altered by the presence of between 0 and 11 sperm per high-power field.

Dysplasia of the cervix is a common problem that is often treated with excision of cervical tissue infected with human papilloma virus. Recent epidemiological studies have reported that loop electrosurgical excision (LEEP) of cervical tissue is associated with cervical stenosis, preterm delivery, and low-birth-weight infants.

Acquired abnormalities

Polyps

Endometrial polyps are benign localized overgrowth glands, blood vessels, and stroma within the uterine cavity.

They mostly originate from the fundal region and extend to the internal os and may be seen single or multiple. Their size differs from a few millimeters to centimeters and may be sessile or pedunculated. There are some risk factors recognized to cause polyps, including age, hypertension, obesity, and tamoxifen use; however, the definite cause of polyps is unknown. The symptoms do not depend on the size, number, or location of the polyps.

Polyps are most often asymptomatic; nevertheless, they commonly cause abnormal vaginal bleeding and infertility. The management of the females with endometrial polyps depends on the symptoms, fertility issues, and risk of malignancy. Polypectomy by means of hysteroscopy is considered as an effective and safe gold standard for both diagnosis and treatment of this condition, especially in case of infertility treatment.

TVS is identified as the best diagnosis tool in this regard; however, it is better to be performed before day 10 of the cycle to decrease the risk of false-positive and false-negative findings. Regarding this, days 4-6 are preferred since the endometrium has its thinnest thickness during this period. It is important to note that sonography needs to be performed by an experienced sonographist because differentiation of polyps from the clot, synechiae, submucosal fibroid, and hyperplasia must be considered for correct diagnosis.

Fibromas

Fibromas are benign tumors of the uterus, which mostly originate from smooth muscle. However, they may contain various amount of fibrous connective tissue. They are the most common pelvic masses among the reproductive aged women, which is found in 20-40% of these population. Although the exact cause of this condition is unknown, these tumors are hormone-related and respond to both estrogen and progesterone. However, several possible risk factors are raised, including age, family history, ethnicity, weight, diet, smoking, pregnancy, and hormone replacement therapy.

Fibromas, which are also known as myomas, leiomyomas, and fibroids, arise within the uterine myometrium, nevertheless, they may be some-times detected in the cervix, ovaries, or broad ligament. Fibromas are classified into three groups based on their location:

1. Intramural fibroids are the most prevalent types, located within the myometrium and totally surrounded by it.
2. Subserosal fibroids are externally extending to the serosa, which can pass to the pelvic cavity and make a “pedunculated uterine fibroma” within pelvic cavity.
3. Submucosal fibroids grow into the endometrial cavity; they are the least common, but the most significant type due to causing more symptoms and infertility.

Myomas can be found either solitary or multiple, ranging in size and location. As a result, regarding the symptoms, they differ from being asymptomatic to having severe symptoms such as infertility. The usual manifestations of myomas entail abnormal uterine bleeding, pelvic pressure or pain, constipation, and urinary symptoms. Infertility may occasionally be observed, which is most often caused by submucosal fibroids. Furthermore, recurrent miscarriages are shown to be relevant to uterine fibroids.

Additionally, some researchers indicated that the probability of the in vitro fertilization failure or pregnancy loss in the patients with distorted endometrium due to myomas, increases up to 50%. Therefore, the accurate investigation of fibromas prior to infertility treatment is essential. The treatment choices vary from expectant management to medical and surgical therapy (e.g., myomectomy or hysterectomy), depending on the patient’s age, symptoms, and reproductive expectation. The recurrency may happen; nevertheless, the likelihood of malignancy is rare.

TVS and transabdominal sonography (TAS) are the primary imaging methods used in the investigation of female pelvis, and the technique of choice in the evaluation of uterine myomas. In experienced hands, the sonographic examination facilitates the detection of the amounts, types, location, and size of the fibromas as well as the amount of endometrial distortion due to myomas, which is very important in the infertility workup. Therefore, these points should be considered in sonography reports. It’s worth noting that in case of small fibromas of less than 5 mm in diameter or in obese patients, the TVS would be more accurate and sensitive than the TAS.

In case of submucosal fibroid and suspected endometrial distortion, it may be difficult to differentiate myoma from polyp. Consequently, further imaging modalities, such as sonohy-sterography or three-dimensional (3D) sonography, are required for detailed investigation. The endometrial thickness has a vital role in the accurate investigation of myomas by 3D TVS. The optimum timing of sonographic assessment of myomas

in this situation is when the endometrium is more than 5 mm in diameter.

Endometrial Hyperplasia

Endometrial hyperplasia is defined as an abnormal proliferation of endometrial glands of various size and shape, which results in thickened endometrium. It occurs following the excess unopposed estrogen stimulation of any source. Polycystic ovarian syndrome patients are more likely to have hyperplasia due to higher circulating estrogen levels. Therefore, a careful endometrial measurement should be performed in this group during the infertility workup. Endometrial hyperplasia is suspected in women presenting with heavy, prolonged, frequent, and irregular uterine bleeding.

When evaluating these patients by TA/TV sonography, we should note that the endometrial thickness and appearance change cyclically due to different phases of menstrual cycle. Therefore, we should ask about the day of the cycle in which the sonography examination was performed. Endometrial hyperplasia will be detected if the endometrial thickness measures ≥ 8 mm during the proliferative phase, ≥ 16 mm during the secretory phase, and ≥ 5 mm during the menopause.

Intrauterine Adhesions

Intrauterine adhesion (uterine synechiae, IUAs) is described as the presence of fibrotic tissue within the endometrial cavity, which causes intracavitary adhesions. It is an acquired condition resulted from trauma to the basal layer of the endometrium usually following curettage or infection. Adhesions range from minor synechiae to severe cohesive adhesions (Asherman's Syndrome). The most common complications associated with IUA are amenorrhea, infertility, recurrent abortions, and preterm birth.

IUA is detected by sonography when the endometrium is thin and irregular. However, the experts believe that TVS has limited use in confirming adhesions. Extra imaging by means of hysterosonography may be helpful in this regard. To confirm the diagnosis, the endometrium needs to be assessed after taking preoperative exogenous estrogen for 4-8 weeks to measure maximal endometrial thickness.

Adenomyosis

Adenomyosis is a common benign condition in which ectopic endometrial glands grow into the uterine myometrium. As a result, myometrial hypertrophy is associated with this disorder. It often occurs in the multiparous women. There are several possible risk factors for this condition including uterine trauma, abortion, chronic endometritis, and hyperestrogenism. The clinical manifestations of adenomyosis are pelvic pain, dysmenorrhea, menorrhagia, menometrorrhagia, uterine tenderness and enlargement, as well as infertility.

The TVS is the first step imaging modality for the evaluation of the women suspected to have adenomyosis. Accordingly, several studies have indicated that TVS has a high sensitivity and accuracy in the diagnosis of adenomyosis, compared to the magnetic resonance imaging (MRI). However, TVS is a skill-dependent tool and the final diagnosis may need to be confirmed by MRI in cases that are uncertain. Adenomyosis should be considered if the following phrases are reported by the sonographist: 1) A normal-sized or enlarged globular shaped uterus, 2) A heterogeneous mottled texture of the myometrium, 3) "Swiss cheese appearance" due to blood clots within the myometrium, 4) Indistinct endometrial line due to disrupted border between the endometrium and myometrium.

Congenital Uterine Anomalies (CUA)

Uterine malformations are a various group of congenital uterine anatomic abnormalities originated from the development defect of mullerian ducts during fetal development. They are associated with higher incidences of infertility, recurrent abortions, intrauterine fetal death, intrauterine growth retardation, pre-mature delivery, fetal malposition, caesarean section, retained placenta, and such gynecological complications as hematocolpos and hematometra. Uterine anomalies are detected in approximately 1-3% of all women; however, 10-25% of the women seek infertility workup.

According to the American Fertility Society classification, these malformations are classified into seven categories as follows: class I includes uterine hypoplasia and agenesis; class II contains unicornuate uterus; class III entails uterus didelphys; class IV consists of bicornuate uterus; class V is septate uterus; class VI includes arcuate uterus; and class VII entails the diethylstilbestrol-related anomalies.

Sonography, in combination with hysteron-salpingography, has an important role in the investigation and classification of the uterine anomalies. In case of no clinical doubt regarding the tubal disorders, TVS can be applied as a more tolerable and less invasive imaging modality. The combination of 3D techniques with TVS gives the specialist the opportunity to investigate the coronal view of the uterus, which configures both endometrium and myometrium together for more accurate diagnosis.

We should note that the optimum timing of ultrasound evaluation and the classification of anatomical uterine disorders are "the secretary phases of menstrual cycle" when the endometrial thickness and echo pattern are better characterized. These anomalies are evaluated at days 11-14 and 17-21 in routine 2D

ultrasound scan of the pelvis and 3D/4D sonography, respectively.

The most commonly found are uterine septums, which are also associated with recurrent pregnancy loss. Interestingly, one study demonstrated that the prevalence of CUA in the fertile and infertile population is the same. Infertility due to CUA is thought to account for roughly 8% of the female causes of infertility; however, 25% of women with a late first trimester or second-trimester miscarriages are found to have CUAs.

In a systematic review and meta-analysis of 21 retrospective and 4 prospective studies involving 3477 women, only the septate uterus was associated with a reduced rate of spontaneous pregnancy. The probability of pregnancy following IVF was not affected by the common congenital uterine anomalies. The risk of spontaneous abortion was significantly increased in women with septate, bicornuate, and unicornuate uteri. Risk for preterm delivery before 37 weeks was increased for all congenital anomalies except for the arcuate uterus. The risk for malpresentation, for example breech presentation, in labor was significantly increased for all anomalies, but most markedly with septate or bicornuate uteri. The risk for fetal growth restriction was greatest with uterus didelphys or bicornuate or unicornuate uteri. The risk for placental abruption was increased for arcuate and septate uteri. A hysteroscopic resection of a uterine septum lowered the risk for miscarriage compared to untreated women with a septate uterus.

Drugs That Cause Infertility in Females

Apart from the causes listed above, some drugs and medicines may also lead to one or more types of infertility in females:

- Psychiatric medications such as antidepressants or antipsychotics
- Steroids such as anabolic or corticosteroids are used to treat lupus or asthma
- Anti-epileptic drugs such as Valproate and Phenytoin
- Thyroid drugs can also affect prolactin levels
- Skin products that contain progesterone or estrogen
- Chemotherapy, especially with toxic alkylating agents

History and Physical

The key aspects of the history of the infertile woman are listed below:

- Duration of infertility
- Obstetrical history
- Menstrual history, to include molimina
- Medical, surgical, and gynecological history to include a history of sexually transmitted infections
- Sexual history to include coital frequency and timing
- Focusing on the male partner, which includes issues with erection and ejaculation
- Social and lifestyle history to include cigarettes, alcohol, and illicit drug use, exercise, and diet, occupation
- Family history, screening for genetic issues, history of venous thrombotic events, recurrent pregnancy loss, and infertility

The physical exam should include the following:

- Vital signs and BMI
- Thyroid evaluation
- Breast exam for galactorrhea
- Signs of androgen excess: dermatological and external genitalia exam
- The appearance of abnormal vaginal or cervical anatomy
- Pelvic masses or tenderness
- Uterine enlargement or irregularity
- Transvaginal ultrasonography is often done at the bedside as part of the initial physical exam

Evaluation

The 5 diagnostic evaluation categories are:

- Semen analysis
- Assessment of ovarian function and reserve
- Assessment of the uterine cavity
- Assessment of the fallopian tubes
- Endocrinological serum studies

Ovarian Function and Reserve

Ovulation can also be detected by a cycle day 21 progesterone serum level, or more accurately, a mid-luteal phase progesterone level. The lab should be taken approximately 1 week before menses, and a progesterone lab value of greater than 3 ng/mL is evidence of ovulation

Assess ovarian Reserve: Cycle Day 3 FSH and estradiol, and Anti-Mullerian hormone (AMH)

FSH levels less than 10 IU/mL demonstrate likely normal ovarian reserve, 10 to 20 IU/mL is intermediate, and an FSH greater than 20 IU/mL is a poor prognosis for spontaneous ovulation due to low ovarian reserve. According to one study, the pregnancy rates per natural menstrual cycle, corresponding to the FSH levels above, are 32%, 17% to 19%, and 3%. Day 3 estradiol less than 80 pg./mL is considered normal with adequate ovarian reserve. Values greater than 80 pg/mL resulted in lower pregnancy rates and values >100 pg/mL had a 0% pregnancy rate

AMH is a hormone expressed by preantral and antral follicles representing a marker of ovarian function that can be measured at any time during a woman's cycle. The AMH levels will gradually decline throughout a woman's natural reproductive life to the point of undetectable levels at menopause. AMH levels seem to be a good predictor of exogenous gonadotropin response:

- <0.5 ng/mL predicts difficulty getting more than 3 follicles to grow
- <1.0 ng/mL shows limited egg supply that may require more aggressive ovulation induction protocols
- to 3.5 ng/mL shows normal values
- >3.5 shows ample supply and may require mild induction to prevent ovarian hyperstimulation syndrome.

Antral follicle counts, measuring the number of follicles less than 9mm in the ovaries with transvaginal ultrasound in the early follicular phase, is also an accurate measure of ovarian reserve and predictive of ovarian response to stimulation.

Tubal Evaluation

Insufflation Test (Rubin's test)

Principle: a tube connects the cervical canal to the peritoneal cavity. Therefore, when pushed through the cervix and enters the peritoneal cavity under pressure, the entry of air or carbon dioxide (CO2) indicates that the fallopian tube is unobstructed (uncommon now). The test should be done in the postmenstrual phase from day seven to day 10 of this cycle. It should not be done in the case of a pelvic infection. Observation: the patency of the tube is determined by: (a) when it rises above 120 mmHg, the pressure drops; (b) a hissing sound is heard during auscultation in any iliac fossa; (c) patient with shoulder pain (air irritates the diaphragm).

Hysterosalpingography (HSG)

It is the most commonly used method as it is non-invasive and cheap. An image intensifier should be used in the X-ray room after the radiopaque dye has been injected into the uterine cavity to inspect the fallopian tubes. A ruby cannula and a Foley catheter should be utilized to see into the uterine cavity and tubes. HSG is usually performed between cycle days 5 and 12. Many centers prepare women for the procedure with an antiprostaglandin agent, like ibuprofen, immediately before the procedure. Injecting a radiopaque contrast material allows for fluoroscopic viewing of the uterine cavity and fallopian tubes during hysterosalpingography. The sensitivity is 84% and the specificity is 75%. The low imaging accuracy of this method is attributed to tubal spasms, but this has been reduced by the use of intravenous scopolamine and patient switching. Additionally, it has been demonstrated that HSG and oily contrast agents have specific therapeutic benefits by eliminating particles from the fallopian tubes. A meta-analysis showed that after HSG, pregnancy and live birth rates increased compared to controls After 24 months, pregnancy rates were 58% and 41% in the HSG and no intervention groups, respectively

The major disadvantages of HSG are that it requires a fluoroscopy imaging device, causes pain during the performance of the procedure, and provides no information concerning the presence of peritoneal diseases, such as endometriosis and ovarian adhesions. HSG is contraindicated in pregnancy, acute pelvic infection, unexplained vaginal bleeding, uterine and cervical cancer.

Principle: A tube connects the cervical canal to the peritoneal cavity. Therefore, when pushed through the cervix under pressure, the radiopaque dye entering the peritoneal cavity indicates that the fallopian tube is unobstructed. Observation: Patency is confirmed by the spillage of dye bilaterally from both the Ostia. In the case of hydrosalpinx, a large mass of dye is seen without a peritoneal spill. A bilateral angle block with dye extravasation is highly indicative of tuberculous salpingitis.

If the HSG demonstrates proximal tubal occlusion, a confirmatory test (selective tubal catheterization or laparoscopy) is required. This additional testing is necessary because about 15% of the cases where HSG demonstrates proximal tubal occlusion are actually due to "tubal spasm" that is physiological and not a permanent anatomical state. The risk of infection following HSG is in the range of 1%.If the HSG demonstrates hydrosalpinges, the patient should be treated with a course of doxycycline.

Hysterosalpingography (HSG) can be performed as a preliminary screening test in the case of suspected fallopian tube infertility in women with no pelvic inflammatory disease or endometriosis. But if a hysterosalpingo-contrast-ultrasonography (HyCoSy) is available, it should be utilized instead. If there are any related comorbidities, the patient should undergo laparoscopic chromopertubation.

Laparoscopic Chromopertubation

The gold standard for the evaluation of tubal patency is laparoscopy with chromopertubation. Laparoscopy is indicated as a first-line diagnostic test for suspected pelvic adhesions, endometriosis, or other pelvic pathologies.

It usually takes place during the proliferation phase. At the same time, laparoscopy is performed, and diluted methylene blue is injected into the uterine cavity to observe the fallopian tube filling and spillage into the abdominal cavity. This surgery has the drawbacks of being expensive, invasive, and requiring anesthesia. Laparoscopy can evaluate the structure of the fallopian tube and the relationship between the fallopian tube and other tissues and organs, accurately separate the fallopian tube adhesion and pelvic adhesion, restore the shape and movement of the fallopian tube and diagnose diseases like pelvic endometriosis. It increases the incidence of secondary infertility in pregnant women. When hydrosalpinx under hysteroscopy indicates tubal obstruction, the guide wire can be directly recanalized

and monitored laparoscopically, and has a good therapeutic effect on the proximal fallopian tube lesions.

Indications for Laparoscopy in Infertility

HSG reveals suspicious results
Before planning for intrauterine insemination
Before planning for ovulation induction
Hydrosalpinx removal before in-vitro fertilization in a suspected case of endometriosis

Sonohysterosalpingography

It is a useful and safe way to access the uterine cavity and check the fallopian tubes' patency. Under ultrasound, about 200 ml of saline is slowly injected through an 8-number foley catheter. The condition of the fallopian tube is confirmed by the flow of saline solution along the tube and is observed by the leakage of fluid from the end of the fimbriae. Unobstructed fallopian tubes can also be confirmed by the free spillage of fluid in the pouch of Douglas. The sensitivity of hysterography and hysterosalpingography to detect hydrosalpinx is 84.6% and the specificity is 99.7%. Hysterosalpingo contrast sonography has progressed from 2D to 3D and even 4D imaging due to the development of contrast agents from negative saline contrast agents to positive microbubble contrast agents. The shell of the microbubble is made of albumin, galactose, lipids, or polymers. The bubble contains a gas that has low solubility in aqueous fluids, such as sulfur hexafluoride or octafluoropropane. The gas in the bubble generates a strong unique signature during ultrasound imaging. The media fills the uterine cavity providing an image of the shape of the cavity and can identify small intracavity filling defects caused by polyps or submucous myomas. If the proximal and distal fallopian tubes are patent, the contrast media flows into the proximal tube and out of the distal tube into the peritoneal cavity. An alternative to an ultrasound contrast media is to use a crystalloid, such as saline, which is vigorously shaken to induce the formation of multiple air bubbles in the saline. HyCoSy is advantageous because patients show better pain tolerance; it avoids the use of contrast agents containing iodine and prevents the use of ionizing radiation.

HyCoSy is performed by cannulating the cervical os and, under ultrasound imaging, injecting an ultrasound contrast media or a crystalloid into the uterus. Specialized ultrasound devices that use contrast-tuned imaging are available to enhance the interpretation of the findings, but standard ultrasound devices can be used for the procedure. Ultrasound contrast media are microbubbles suspended in a solution. HyCoSy is an office-based procedure that is performed in the early follicular phase. HyCoSy is associated with less pain than HSG. HyCoSy has sensitivity to detect tubal disease similar to HSG, but is superior to HSG for the detection of small intracavitary lesions.

Falloscopy

It is used to study the complete length of the fallopian tube lumen with the help of thin and flexible fiber optic equipment. It is done through the uterine cavity using a hysteroscope. It helps to directly observe the fallopian tube orifice, mucosal pattern, polyps, or fragments in the fallopian tube.

Salpingoscopy: The lumen of the fallopian tube is visualized by introducing a rigid endoscope through the bristles of the tube.

Uterine Cavity

The gold standard for assessing the uterine cavity is hysteroscopy, which allows direct visualization of the intrauterine pathology and provides an opportunity for immediate surgical correction. Although hysteroscopy is considered the gold standard, a less invasive approach is more commonly utilize with a saline infusion sonogram (SIS). The SIS is highly sensitive and specific for all intrauterine abnormalities and is adequate as a screening tool before infertility treatment, with or without 3-D model rendering. Hysterosalpingography (HSG) is the radiographic examination of the uterus and fallopian tubes and is regarded as the gold standard for assessing the fallopian tubes, providing accurate information on their patency and shape. Limitations to hysterosalpingography are seen in identifying uterine factors affecting fertility in most findings. Other radiographic examinations such as the ultrasound scans should be used alongside in evaluating findings of infertility as it gives precise description of the outline of the uterus and can capture intramural myoma which isn't easily seen on hysterosalpingogram scans hence the importance of combining these radiographic evaluations.

Infertility Tests That Should Not Be Routinely Ordered

- Laparoscopy for unexplained infertility
- Advanced sperm function testing (eg., DNA fragmentation testing)
- Postcoital testing
- Thrombophilia testing
- Immunologic testing
- Karyotype
- Endometrial biopsy
- Prolactin

Treatment / Management

Lifestyle Changes

Women with extremes in body mass index (BMI) frequently present with infertility and ovulatory dysfunction. Women with a BMI of less than 17 kg/m^2 with a history of intense exercise regimens or women with eating disorders are likely to develop hypogonadotropic hypogonadism, which causes deceased pituitary gonadotropin secretions. In The United States, controlled ovarian stimulation using exogenous gonadotropins are used to induce ovulation; however, in Europe, women who fail to respond to

therapy can receive pulsatile GnRH therapy. One study demonstrated the importance of behavioral change in inducing ovulation. Of the women who received individual directed therapy to correct energy deficiencies or behavior problems, 87% resumed regular ovarian function to correct the abnormal BMI.

Women with a BMI greater than 27 kg/m^2 with anovulation can improve ovulation with weight loss alone. Multiple studies have shown that a loss of 10% of body weight will restore normal ovulation in 50 to 100% of women in less than 1 year. Even though weight loss is important for many aspects of a patient's life, one study showed that obese women who received counseling and interventions for weight loss before infertility treatment did not have higher pregnancy or live birth rates compared to obese women who had infertility treatment without weight-loss interventions. Therefore, a specific BMI is not required to initiate fertility treatment.

Controlled Ovarian Hyperstimulation

The first-line medication for infertility of unknown origin and the medication most providers use is clomiphene citrate (CC). Clomiphene is a selective estrogen receptor modulator (SERM) with estrogen antagonist and agonist effects that ultimately increase gonadotropin release from the anterior pituitary. Clomiphene effectively treats WHO class 2 anovulation but ineffective in WHO class 1 and class 3 anovulation. Clomiphene is dosed starting at 50mg starting on cycle day 2, 3, 4, or 5 for 5 sequential days. The couple is encouraged to have intercourse every other day for one week, beginning 5 days after the last pill. However, the odds for pregnancy may be increased when clomiphene is combined with intrauterine insemination (IUI). There is little difference in the results of ovulation, pregnancy, or live birth regarding which day the medication is started, between cycle days 2 to 5.

Another commonly used oral medication for ovulation induction is letrozole. Letrozole is an aromatase inhibitor that prevents estrogen production by preventing the conversion of androstenedione and testosterone to estrone and estradiol. Letrozole is FDA indicated for the extended adjuvant treatment of breast cancer, and its use for ovulation induction is considered off-label. However, there is an abundance of scientific literature and multiple committee opinions that support both the efficacy and safety of its use in ovulation induction. Letrozole is dosed starting at 2.5, 5, or 7.5 mg/day on cycle days 3, 4, 5, 6, 7 with intercourse every other day 5 days after completing the medication, which is similar to clomiphene. According to ACOG, letrozole should be considered the first-line treatment for women with PCOS over clomiphene.

The benefits of letrozole over clomiphene are:

- Higher rate of monofollicular development and a corresponding decrease in twin gestations
- Shorter half-life
- No antiestrogenic effects on the endometrium and central nervous system
- Lower estradiol levels, which is a benefit for women with breast cancer undergoing IVF

Gonadotropin therapy is a more intensive medical regimen used for WHO Class 1, 2, or 3 anovulatory disorders. Gonadotropins are beneficial as a second-line treatment option for women who failed to conceive after multiple cycles of clomiphene. There is one study that showed an increased live birth rate with gonadotropins compared to continued clomiphene usage. Transvaginal ultrasounds are used to monitor follicular growth every 2 to 3 days during the late follicular phase to evaluate mature follicles. A mature follicle is greater than 18mm in diameter and estradiol of greater than 200 pg./mL. Once a mature follicle is identified, recombinant HCG 250mg subcutaneous injection or intramuscular injection of 10,000U of urinary-derived HCG is given to trigger ovulation. Once the trigger shot is given, an IUI occurs 24-36 hours later. IUIs can be used in combination with all the ovarian induction agents, and IUI with medication is encouraged to increase pregnancy rates. There is unclear evidence as to the superiority of allowing a natural LH surge versus HCG trigger before IUI. A meta-analysis completed in 2010 showed no clear evidence of one treatment option over the other, and the treatment choice should be based on cost, hospital staffing restrictions, and patient convenience.

Tubal Surgery

After diagnostic testing has indicated tubal occlusion, interventional radiology and microsurgical techniques can restore fallopian tube anatomy and function.

Proximal Tubal Occlusion

Proximal tubal blockage accounts for 10% to 24% of tubal disease.34 Selective salpingography is a radiographic procedure similar to HSG in which the fallopian tube is directly opacified under fluoroscopic guidance. A catheter is placed in the tubal ostium, and a radiopaque dye is injected into the fallopian tube to determine patency.

The procedure is usually performed by interventional radiologists and has been used to differentiate tubal spasm from true tubal obstruction. The advantage of this procedure is that if an obstruction is identified, a subsequent fallopian tube recanalization can be performed during which a smaller catheter is placed to clear the obstruction.

The recanalization procedure is simple and successfully completed in 71% to 92% of cases. Recanalization is possible but less successful in women who have occluded tubes after surgical anastomosis for reversal of a tubal ligation. Reported success rates per fallopian tube are related to amount of postoperative scarring and range from 44% to 77% Of the women who

had successful fallopian tube recanalization, the average pregnancy rate was 30%. Complications from the procedure are rare and include perforation in 3% to 11% of cases without clinical sequelae and an ectopic pregnancy rate of 3%, which is comparable with the general population. If the obstruction is not resolved by tubal cannulation, then in vitro fertilization (IVF) is preferred to proximal tube resection and microsurgical proximal tube anastomosis. Microsurgical proximal tube anastomosis has been largely relegated to historic surgical interest, because it is associated with very low success rates and risk of cornual rupture in pregnancy. It should only be considered if IVF is not an option for the patient.

Distal Tubal Occlusion

Distal tubal occlusion accounts for most tubal occlusion and infertility. Microsurgery can treat most cases depending on the degree of occlusion. A successful outcome with tubal surgery is associated with no more than limited filmy adnexal adhesions; mildly dilated tubes (<3 cm in diameter) with thin and pliable walls; and a lush endosalpinx with preservation of the mucosal folds. Salpingostomy involves creating an opening in a completely obstructed tube, and historically was performed at laparotomy with microscopic assistance. More recently, laparoscopic salpingostomy has been performed with equivalent results. Unfortunately, salpingostomy yields low long-term pregnancy rates of approximately 20% to 30% 1 to 2 years after surgery; rates vary considerably depending on the extent of tubal damage and other clinical factors. Ectopic pregnancy rates after salpingostomy range from 4% to 25%.

Varying degrees of fimbrial disease can be laparoscopically treated with fimbrioplasty and fimbriolysis. Fimbriolysis refers to the separation of adherent fimbria. Fimbrioplasty describes the correction of phimotic but patent fimbria. Surgical success is inversely related to the severity of disease. For mild forms of distal tubal occlusion, pregnancy rates have been reported up to 60%,45 but success rates are lower at 10% to 35% for women with severe tubal disease. Most of the pregnancies occur within the first 2 years after surgical treatment of distal tubal disease. There is almost no role for surgical intervention in patients with proximal and distal disease because live birth rates are invariably lower than 10%.

Hydrosalpinges

Distal tubal occlusion from salpingitis or extrinsic causes may lead to formation of hydrosalpinges either in one or both fallopian tubes. Numerous studies have shown that hydrosalpinges have a negative effect on pregnancy and IVF success rates. In a large meta-analysis of retrospective cases, women with hydrosalpinx had half the pregnancy, implantation, and delivery rates, and up to twice the incidence of spontaneous abortions after IVF and embryo transfer (IVF-ET). Although the hydrosalpingeal fluid does not have direct toxic effects on the human embryos, leakage of the fluid into the uterine cavity may compromise implantation through decreasing endometrial receptivity and mechanically washing the blastocyst from the endometrial surface. Treatment options for hydrosalpinges include drainage, neosalpingostomy, salpingectomy, and proximal tubal occlusion.

The least invasive of these options is transvaginal needle aspiration of a hydrosalpinx under ultrasound guidance before an IVF-ET cycle or at the time of oocyte retrieval. Therapeutic aspirations of hydrosalpinges have been reported; however, there is often rapid reaccumulation of fluid. Nonrandomized study results were conflicting and conclusions weak. One randomized controlled trial (RCT) reported improved pregnancy outcomes, but this study was underpowered, leaving the need for more studies to assess the benefits and outcomes of hydrosalpinx aspiration. Laparoscopic neosalpingostomy for draining hydrosalpinges before IVF-ET theoretically should improve pregnancy rates, but there are no confirmatory studies to date. Randomized clinical trials comparing pregnancy rates and outcomes with IVF in women with and without prior laparoscopic salpingectomy have consistently reported that salpingectomy restores pregnancy rates and live birth rates to those similar to women without hydrosalpinx. The multicenter, prospective RCT by Strandell and colleagues found significantly increased pregnancy and live birth rates of 37% and 29%, respectively, in the salpingectomy group compared with rates of 24% and 16%, respectively, in the nonintervention group. A Cochrane analysis of the three RCTs concluded that laparoscopic salpingectomy should be considered before IVF for women with communicating hydrosalpinges. Meta-analysis of two laparoscopic proximal tubal occlusion studies also found improved odds of clinical pregnancy. Thus, both salpingectomy and proximal tubal occlusion are recommended for the treatment of hydrosalpinx before IVF-ET.

Sterilization Reversal

Approximately 1 million women in the United States have tubal ligations each year. Up to 7% regret the permanent sterilization, and about 1% request tubal reversal. For those women who want to conceive, there are two treatment options: IVF or tubal reanastomosis. The advantages of surgical tubal reanastomosis are the chance for natural conception and lower risk for multiple gestations, but the disadvantages are the potential tubal scarring from the surgery itself, delay in attempting conception, higher risk of ectopic pregnancy, and need for future contraception. Tubotubal reanastomosis is traditionally achieved by laparotomy after laparoscopic assessment of the fallopian tubes. If one or both fallopian tubes are judged to be repairable, then the occluded ends of the proximal and distal segments are opened and the ends are anastomosed with a fine nonreactive suture. Koh and Janik reported the first case of laparoscopic

tubal reanastomosis in 1992, but only laparoscopists skilled in microsurgical reanastomosis have been able to successfully replicate the procedure. More recently, more surgeons are using the da Vinci Robotic Surgical System for laparoscopic tubal reanastomosis with good results. Women with tubal occlusion caused by tubal ligation are typically fertile and have better success rates after tubal surgery than women with tubal pathology. They also have good success rates with IVF. A preoperative HSG may be useful to assess the proximal segment of the tube. Less than 5% of fallopian tubes are irreparable. The prognosis for achieving live birth after tubal reversal depends on the patient's age, type and location of the sterilization procedure, and the final length of the repaired fallopian tubes. Better success rates are reported in younger women with no other infertility factors, and sterilization performed with rings or clips. In appropriately selected candidates, overall conception rates are good (62%–83%) after microsurgical sterilization reversal. The risk for ectopic pregnancy after tubal reanastomosis is up to 6%, and higher after isthmic-ampullary anastomosis than after isthmic-isthmic anastomosis. Sterilization reversal after hysteroscopic placement of the microinserts Essure and Adiana is very difficult to achieve because of the placement of the coils, which scar and occlude the isthmic portions of the fallopian tubes. Sterilization reversal of this type requires tubouterine implantation in which a new opening is created through the uterine muscle and the remaining tubal segment is inserted into the uterine cavity. During the same procedure the microinserts are removed. Data on the success rate of tubal reversal after intratubal microinserts are limited. Three case reports of successful tubouterine implantation after intratubal microinserts have been described.

Uterine Abnormalities

There is unclear evidence on the effect of leiomyomas on infertility and live birth rates. It is recommended that the patient receive a complete infertility workup prior to further investigation into fibroids. The most important aspect of fibroids is the location. Fibroids that impinge on the endometrium and distort the uterine cavity result in impaired implantation and increased miscarriage rates. Women with submucosal or submucosal-intramural fibroids that distort the uterine cavity have been proven to have decreased pregnancy rates. With the removal of these fibroids, pregnancy and live birth rates increase. The first-line treatment for removal of the most detrimental fibroids is operative hysteroscopy. Other uterine pathologies like uterine synechiae and septa are more related to recurrent pregnancy loss but are capable of causing infertility. Operative hysteroscopy has shown a marked reduction in pregnancy loss for women with both synechiae and septa. Asymptomatic polyps have also been shown to cause infertility. One study showed a polypectomy on asymptomatic infertile women before IUI increased pregnancy rates from 28% to 63%.

Advancements in Reproductive Surgery with the Da Vinci Surgical System

The da Vinci Robotic Surgical System developed by Intuitive Surgical (Sunnyvale, CA) pioneered one of the first integrated three-dimensional viewing systems for minimally invasive surgery. The system was approved for laparoscopic hysterectomies in 2005, but since that time has expanded to include myomectomy, complex resections of endometriosis, sacral colpopexy, and tubal reanastomosis. The high-definition video system and three-dimensional viewer have tremendously enabled surgeons to perform laparoscopic microtubal surgery with good results. Gargiulo and Nezhat75 reported their experience with a variety of robotic-assisted gynecologic surgeries including robotic-assisted tubal reanastomosis and tubal reconstructive surgeries citing the three-dimensional visualization of the operative field, decreased surgeon fatigue, and the seven degrees of motion provided better dexterity and surgical precision. Logically, using the da Vinci Surgical System for the technically challenging and microscopic procedures in reproductive surgery has been a natural progression for this surgical tool. Techniques for the robot-assisted tubal reanastomosis and other complex surgical procedures are described in recent publications. A series comparing outcomes between women undergoing robotic-assisted tubal anastomoses and open microsurgical tubal anastomosis demonstrated that the robotically assisted laparoscopic microsurgical tubal anastomosis was feasible and cost effective with results equivalent to the traditional open approach. In a series of 10 women with prior bilateral tubal ligation, 19 fallopian tubes were reanastomosed using the robotic-assisted laparoscopy technique. Chromopertubation at the end of the surgery demonstrated patency in all tubes. At 6 weeks after surgery HSGs were performed, and 17 of 19 tubes were patent. Five intrauterine pregnancies were reported. The advantages of the da Vinci Surgical System are clear, and it has the potential to revolutionize the field of reproductive surgery.

In Vitro Fertilization

Procedures

Step 1 is controlled ovarian hyperstimulation with injectable gonadotropins, most commonly. Thirty-six hours after a trigger shot, or HCG injection, a specialist will perform a transvaginal ultrasonography-guided needle aspiration and oocyte retrieval. After retrieval, the oocytes are transferred to a special media, and normal sperm is transferred to the dish for insemination. If there is abnormal sperm, intracytoplasmic sperm injection (ICSI) is performed. ICSI is a procedure that places a single spermatozoon directly into the egg cytoplasm. After fertilization, the embryo is assessed and graded. The embryos are then transferred on Day 3 or Day 5. Preimplantation genetic testing (PGT) is an additional IVF procedure that helps detect known parental genetic mutations or balanced translocation. Additionally, PGT can also be used to

detect aneuploidy, both monosomies and trisomies, from all 23 chromosome pairs. Apart from a known parental carrier for a genetic mutation or balanced translocation, PGT likely is beneficial for advanced maternal age, repeated IVF failures with high-grade embryos, recurrent pregnancy loss, and unexplained infertility.

As assisted reproductive technologies (ART) have improved over the past few decades, almost all causes of infertility, especially tubal factor infertility, have been treated though ART techniques. In the past decade alone, the percentages of transfers that resulted in singleton live births have increased from 26% in 2000 to 35% in 2009. The results of IVF-ET and tubal surgery are difficult to compare because surgery and IVF-ET have variable results depending on the surgeon and IVF clinic. One prospective RCT comparing tubal surgery to infertility with IVF-ET as first-line therapy found that the former was associated with lower costs and higher overall pregnancy rates. However, a Cochrane analysis concluded that the success of tubal surgery versus IVF remains largely unknown, and in the treatment of women with tubal factor infertility, there are no RCTs comparing IVF-ET with tubal surgery. When a couple is deciding between IVF-ET or tubal surgery, the advantages and disadvantages of both should be discussed. The advantages of IVF-ET are good per cycle success rates, it is less surgically invasive, and attempts at conceiving can start Tubal Factor Infertility immediately. Disadvantages of IVF are risk of multiple gestations, ovarian hyperstimulation, and high cost. Some adverse perinatal outcomes have been associated with pregnancies conceived through IVF, such as perinatal mortality, preterm delivery, low and very low birth weight infants, intrauterine growth restriction, and congenital malformations. Nevertheless, women who are older, women with severe tubal disease, couples with male factor infertility, and couples who may only want one or two children should be counseled toward infertility management with ART. Patient preference, religious beliefs, cost, and insurance reimbursement also play a role in management.

In vitro fertilization (IVF) is the first-line treatment for bilateral tubal factor infertility. Tubal corrective surgeries have worse pregnancy outcomes and have an increased risk of ectopic pregnancy. Women with severe tubal disease, including hydrosalpinx, are encouraged to have a bilateral salpingectomy to increase the pregnancy rate of IVF. For women with mild distal tubal disease, fimbrioplasty is an option to allow for multiple pregnancies without IVF. One small study showed that the pregnancy rate was equal to IVF for mild tubal disease, but the risk of ectopic pregnancy was 15% compared to 0.7% for IVF treatment. The patients with a prior bilateral salpingectomy or tubal ligation for contraception are an important tubal factor population. It is always important for healthcare providers to discuss the risk of regret with all women who desire tubal ligation. The chance of pregnancy after tubal reanastomosis depends on the patient's age, the type of ligation, and the tubal length available. Younger women who had a ring or a clip with more than 4 cm of tubal length are the best candidates and have comparable pregnancy rates to IVF. However, the time to pregnancy is significantly longer following tubal surgery as compared to IVF.

Differential Diagnosis

Infertility is a highly complex disorder with significant effects on the couple as a whole. It is important to remember that there can be, and regularly are, multiple causes of infertility. The differential diagnosis for infertility can be extensive, and a thorough workup is required to ensure no harmful disease process is missed. Due to the expansive nature of this discussion, the manuscript will focus on the differential diagnosis for PCOS due to its high prevalence in the infertile population.

The differential diagnosis for patients with suspected PCOS includes:

- Androgen producing ovarian tumors
- Adrenal tumors
- Nonclassic congenital adrenal hyperplasia
- Cushing syndrome
- Prolactinemia disorders
- Thyroid disorders

The investigation of PCOS should include total testosterone, DHEA-S, and 17-Hydroxyprogesterone for evaluation of a virilizing ovarian or adrenal tumor or nonclassical congenital adrenal hyperplasia (CAH). There is a suggestion that DHEA-S should only be reserved for women with severe virilization because an asymptomatic, slightly elevated DHEA-S level does not affect management. Additionally, prolactin and thyroid-stimulating hormone should also be measured.

- The upper limit of normal for female testosterone is 45 to 60 ng/dL
- A testosterone value greater than 150 ng/dL warrants investigation for ovarian and adrenal androgen-secreting tumors.
- DHEA-S of greater than 500 to 700 mcg/dL warrants further investigation of an adrenal tumor.
- A fasting 17-hydroxyprogesterone greater than 200 ng/dL collected during the follicular phase warrants an ACTH stimulation test, and a value greater than 500 ng/dL is diagnostic for nonclassical congenital adrenal hyperplasia.

Prognosis

This section will cover the pregnancy rates per cycle for each of the treatment modalities. The data are mostly from the evaluation of unexplained infertility but is also consistent for known causes of infertility. The rates of IVF will vary drastically according to multiple individual factors. The following pregnancy rates

were collected from a retrospective analysis of 45 separate studies

- No treatment: 1.3% to 3.8%
- IUI alone: 4%
- Clomiphene citrate (CC) alone: 5.6%
- CC with IUI: 8.3%
- Gonadotropins alone: 7.7%
- Gonadotropins with IUI: 17.1%
- IVF: 20.7%

Letrozole alone and letrozole with IUI result in similar pregnancy rates as CC plus IUI and can be used for women who IVF is not an option and have failed CC plus IUI.

In 2009, a study showed that women who failed CC plus IUI should go straight to IVF instead of gonadotropins plus IUI prior to IVF. This study resulted in less time to achieve pregnancy, fewer treatment cycles, and lower total financial cost per delivery. The IVF pregnancy rates have increased since the paper reported above; however, the data still proves that IVF results in the highest pregnancy rates of all treatment options.

The research above suggests that providers can use clomiphene alone as a first-line treatment for infertility. This is no longer true. In 2008, a randomized control trial showed that clomiphene alone had lower live birth rates than expectant management, respectively 14% and 17%. This paper did show that there is a benefit regarding patient satisfaction versus expectant management; however, a majority of women in both categories were satisfied with their care. In light of this study, ASRM published a committee opinion stating that clomiphene with timed intercourse should be discouraged as a first-line treatment for unexplained infertility

Complications

The three primary complications associated with infertility treatments are multiples, ectopic pregnancy, and ovarian hyperstimulation syndrome.

Multiple Gestations

The risk of multiples has been a problem for artificial reproductive technologies since the inception of the practice. In the U.S., 32% of ART pregnancies were multiples compared to 3.4% of naturally conceived births. In 2009 according to the CDC, the chances of singleton, twin, or higher-order pregnancies with IVF fresh embryo transfer were 62%, 29%, 3%, respectively. The oral ovarian induction agents, clomiphene and letrozole, have a lower risk of multiple gestations compared to gonadotropins with the percentages of twins, triplets, and quadruplets of 7%, 0.5%, 0.3%, respectively. Gonadotropins have a 13% chance of multiple gestations, including triplets.

Currently, the ASRM and CDC have strongly promoted the use of elective single embryo transfer ESET for good prognosis patients. With the use of ESET, the rates of twins and triplets dropped to less than 1%. Additionally, there is active debate if gonadotropins should be used for ovulation induction outside of an IVF protocol due to the high risk of multiples. As the use of IVF increases, the use of gonadotropins in conjunction with IUI will likely continue to decrease.

Ectopic Pregnancy

Ectopic pregnancy following treatment of infertile patients is another risk, which requires extensive counseling. There is a two-to threefold increase of ectopic pregnancies among infertility patients. This is thought to be associated with a high percentage of tubal factor infertility. The highest associated risk of ectopic pregnancy is after a tubal surgery to correct tubal factor infertility. Rates of ectopic pregnancy following tubal reconstructive surgery is approximately 9%, with other reports as high as 30%. The risk of ectopic pregnancy with IVF fresh embryo transfer is higher than frozen embryo transfer, but the overall rate of ectopic pregnancies with IVF is roughly 1.3%. There does not seem to be an increase in ectopic pregnancies with the use of ovulation induction agents combined with IUI versus natural conception; however, in a large study comparing the ovulation induction agents: clomiphene, letrozole, and gonadotropins had ectopic pregnancy rates of 4%, 6%, and 8%, respectively.

Ovarian Hyperstimulation Syndrome (OHSS)

This is an iatrogenic complication of controlled ovarian hyperstimulation that results in a broad range of signs and symptoms, ranging from abdominal distention, nausea, vomiting, enlarged ovaries, third-spacing of fluids, renal failure, and venous thrombosis, acute respiratory distress syndrome, electrolyte derangements, cardiac arrhythmias, and sepsis. If severe OHSS is not treated and monitored, mortality can result from the listed complications. The different stages of OHSS are classified by Golan *et al*., in 1989. The underlying pathophysiological feature is increased capillary permeability, resulting in a fluid shift into the third space. Women at the highest risk of developing OHSS are those patients with greater than 20 mature follicles who also receive an HCG trigger shot. The incidence of moderate and severe OHSS with IVF ranges from 6% to 1%, respectively. The diagnosis, prevention, and management of OHSS are outside the scope of this manuscript.

Deterrence and Patient Education

Women should see their providers for a referral to an infertility subspecialist if they are unable to achieve pregnancy after 1 year of unprotected timed intercourse, or if she is older than 35 years of age, 6 months of unprotected timed intercourse. It is important to explain that infertility can result from both female and male factors or a combination of the two. This is important to

remember, as most couples with infertility seek care through the female partner's health provider, potentially overlooking the male contribution. The medications and procedures available for female infertility are well studied and have a well-known risk profile. The patient needs to be aware of the risk of multiple gestations, ectopic pregnancy, and OHSS. Finally, the patient needs to understand the odds of pregnancy per treatment cycle for each modality. The inability to conceive, even with IVF, is a possibility that needs to be fully understood before dedicating a large number of resources required for infertility treatment

Enhancing Healthcare Team Outcomes

As mentioned at the beginning of this article, infertility is a devastating diagnosis and should be considered a disease process by all healthcare team members. The the best way to improve the physical, emotional, social, and interpersonal stressors of infertility for the patient is to complete an immediate and thorough investigation into both partners. The evaluation is straightforward and can be completed before referral to a fertility subspecialist. This will expedite and enhance the specialist's ability to initiate follow-up studies and treatments. The use of either clomiphene or letrozole with timed intercourse alone can be used to correct a known cause of anovulation but should not prolong the referral to a subspecialist. All primary care providers need to set realistic expectations of the chances of pregnancy and the possibility of complications when counseling couples suffering from infertility.

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