

## Infertility: Etiology, Pathophysiology, and Treatment Options. A Review

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### Abstract

Infertility is a term used to describe a pathological condition that can affect married relationship in more than one line, it means the women don't have pregnancy after twelve months of successful sexual relationship. Infertility could be primary or secondary and the main causes include ovulation fault, ovum transport problems, and implantation failure. There are many mean to early diagnose infertility and specialize it cause to decide proper treatment intervention. Infertility can result from men or women causes and for each case suitable treatment options are present now. Now a day, there are different interventions that can help couples to have successful conceive such as Intra-Uterine Insemination, In-vitro fertilization, Donor egg and sperm in addition to the medications. Finally, infertility could result in a health, social, and economic complication if not diagnosed and treated early.

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## العقم: الأسباب والعوامل المرضية وخيارات العلاج

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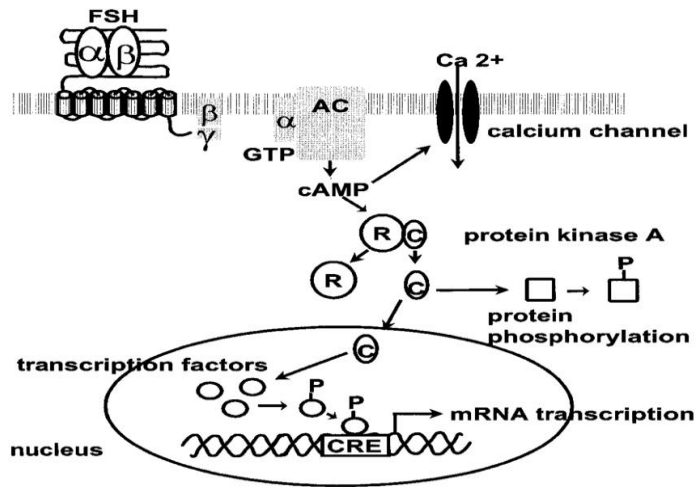
### الخلاصة

العقم هو مصطلح يستخدم لوصف حالة مرضية يمكن أن تؤثر على العلاقة الزوجية بأكثر من طريقة، وهذا يعني أن المرأة لا تحمل بعد اثني عشر شهرًا من العلاقة الجنسية الناجحة. يمكن أن يكون العقم أوليًا أو ثانويًا وتشمل الأسباب الرئيسية خطأ التبويض ومشاكل نقل البويضة وفشل الانغراس. هناك العديد من الوسائل لتشخيص العقم في وقت مبكر وتخصص أسبابه لتحديد التدخل العلاجي المناسب. يمكن أن ينتج العقم عن أسباب تتعلق بالرجال أو النساء وفي بعض الحالات توجد خيارات علاج مناسبة الآن. في الوقت الحاضر، توجد تدخلات مختلفة يمكن أن تساعد الأزواج على الحمل بنجاح مثل التلقيح داخل الرحم والتخصيب في المختبر وبويضات المتبرع والحيوانات المنوية بالإضافة إلى الدواء. أخيرًا، يمكن أن يؤدي العقم إلى مضاعفات صحية واجتماعية واقتصادية إذا لم يتم تشخيصه وعلاجه مبكرًا.

# 1. Infertility

Infertility is a term used to describe women who cannot become pregnant after one year or more of non-protective sex (Sezgin, Hocaoglu and Guvendag-Guven, 2016). It could be divided up into primary and secondary types according to whether a woman had a previous pregnancy or not (Vitale et al., 2016). It is a common problem of most countries in the world, affected about 11 – 26% of Iraqi married women with age range of 20 – 40 years (Bosch et al., 2021). Follicle-stimulating hormone (FSH) and luteinizing hormone (LH) have integration roles in the up growth of follicles and ovulation via a complex coordination of the hypothalamus – pituitary - reproductive organs and oocytes (Sezgin, Hocaoglu and Guvendag-Guven, 2016). The factors affected women infertility involve failure of premature ovaries, endometriosis, polycystic ovarian syndrome (PCOS), uterine fibroids, and endometrial polyps. Many hormones like thyroid stimulating hormone (TSH), FSH, LH, and prolactin affect normal follicle development and ovary production functions; any increase or decrease in the releasing of these hormones or interfering with action of these hormones on them receptors may lead to irregular menstrual cycles and low fertility and ovulation diseases (Vitale et al., 2016).

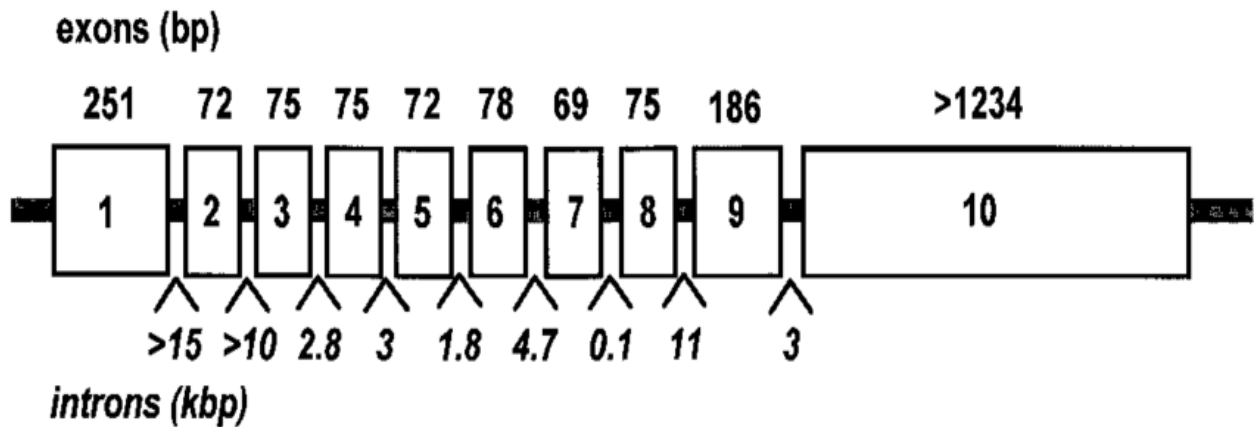
FSH had a stimulatory and trophic effects on gametogenesis. This effect occurs by binding of FSH to a specific G protein - coupled receptor which occasionally located on cellular surface of ovarian granulosa. The main signal transduction mechanism of this receptors (FSHR) are stimulation of adenylate cyclase enzyme and increase of cAMP levels inside the cells, activation of intracellular calcium, stimulation of the mitogen-activated protein kinase (MAPK) enzyme, and the stimulation of inositol triphosphate (IP3) production (Sezgin, Hocaoglu and Guvendag-Guven, 2016) as illustrated in Fig.1.



**Figure 1:** Model of Signal Transduction Pathways of The FSH Receptor (Vitale et al., 2016).

Hormones are chemical messenger that synthesize inside human body and secreted from special gland to do a special biological function. These compounds have a great role in regulation a multiple body physiological function. Since they are secreted to the target tissue by blood stream after secretion from the glands (Bosch et al., 2021). One of the most important hormones are called sex hormones such as Follicle Stimulating Hormone (FSH). This hormone is synthesized and secreted from the interior pituitary gland and affect the targeted cells by interacting with a special receptor called FSHR. FSH has a crucial role in regulating number of sexual system functions such as the proliferation of granulosa cells, inducing of secondary follicle. The

reading of the FSH analysis is considered normal. If the results of the test for female in pre-pubertal are (0-4.0IU/L), in Puberty range from (0.3-10 IU/L). In adult female, menstruation ranges from (4.7-21.5IU/L) (Sezgin, Hocaoglu and Guvendag-Guven, 2016). The FSHR gene has 10 exons and 9 introns and is found on chromosome 2 (p21-p16). The extracellular domain of the receptor is encoded by the first 9 exons, while the C-terminal end of the extracellular domain, the whole trans membrane domain, and the intracellular domain of the FSHR are all encoded by exon 10. Although exon 10 is essential for signal transduction, ligand binding is not dependent on it. Currently, the National Centre for Biotechnology Information (NCBI) SNP database contains information on around 1,800 SNPs affecting the FSHR gene (Sezgin, Hocaoglu and Guvendag-Guven, 2016). The structure of FSHR gene is shown in Fig.2.



**Figure 2:** Structural Organization of The Human FSH Receptor Gene (Sezgin, Hocaoglu and Guvendag-Guven, 2016)

## 2. Epidemiology: Incidence & Prevalence

The definition of "infertile" in the Oxford English Dictionary is "not able to have babies or produce young," which suggests a state of infertility rather than "difficulty of getting pregnancy," which corresponds to the opinion of many specialists (Sezgin, Hocaoglu and Guvendag-Guven, 2016). Other scientific paper explains the term infertility as the incapability to become pregnant after twelve months of efficient sexual activity with no protection or shield. The majority of European nations have registered a continuous fall in birth rates since the early 1950s, with no significant differences statically among regions or socioeconomic classes. A little more than 15% of people in high-income countries and 9% to 30% of those in low-income countries, respectively, suffer from infertility (Sezgin, Hocaoglu and Guvendag-Guven, 2016; Vitale et al., 2016; Bosch et al., 2021). According to previous studies, in underdeveloped countries about one of each four couples suffering infertility. While about one in each seven married women have infertility in developed countries who are in childbearing age. In several global parts, the incompetence rate may be higher than 30% such as Sub-Saharan Africa and South Asia, the Middle East and North Africa, Central and Eastern Europe, and Central Asia (Sezgin, Hocaoglu and Guvendag-Guven, 2016). In general, South East and Sub-Saharan Africa are considered the highest region of infertility rate. Infertility can have a variety of reasons and manifestations, according to reports from several African nations (Sezgin, Hocaoglu and Guvendag-Guven, 2016; Vitale et al., 2016; Bosch et al., 2021).

There are many statistics on infertility in high-income nations and other African nations, but few on infertility in Sudan. With a population of 36,787,000, Sudan is the third-largest nation in Africa. Infertility statistics are inadequate in this country since there is no sufficient government centers of reproductive problems. Despite that, a study of infertility includes only 10 states recorded 11.5 % of couples were having infertility with female causes in most cases (Abdullah, Ahmed and Oladokun, 2021; Bayoumi et al., 2021). Data from community centers show that up to 30% of Nigerian couples have troubles or difficulties to become pregnant even after two years of married without using any contraceptive means. Infertility, which is linked to depression, anxiety, disordered eating habits, sexual dysfunction, and interpersonal relationships, affects 5–10% of women in reproductive age. Numerous of these risk factors can be avoided (Okonofua et al., 1997; Tabong and Adongo, 2013; Agbana, Michael and Ojo, 2023). Other study carried out at Kamal AL-Samarai hospital in Iraq shows that the greatest number of infertile women were between the ages twenty-five and thirty-five years, and 42 (36.64%) of those who were infertile were illiterate, while 25 (21.7 percent) and 19 (16.6 percent) had secondary and primary education levels, respectively. Same study also revealed that primary infertility was more common than secondary infertility, with 77 (66.9%) primary infertility cases outnumbering 38 (33.1%) cases (Al-Kareem et al., 2022). Additionally, compared to obese and overweight infertile women, 32 (27.8%) and 30(26.1%), respectively, 53 (46.1%) were normal. Additionally, 77(66.1%) women live a good life with their husbands and family. In addition, the findings show that primary infertility increased to 21 (18.3%) from 16 (13.9%) secondary infertility and between two and three years, primary infertility increased to 45 (39.13%) from 12 (10.4%). Secondary infertile women, 69(60%) lived in urban areas compared to rural 46(40%) (Abebe, Afework and Abaynew, 2020; Chemaitelly et al., 2021; Sharifi, Azizi and Roudsari, 2022).

### **3. Etiology of Infertility**

As stated by the Centers for Disease Control and Prevention stated in 2013, there are three main categories that can be used to categorize the causes of female infertility: fail of ovulation, transport problems, and implantation difficulties. The details of these categories are covered in more details below (Bosch et al., 2021):

**3.1.First: Faulty Ovulation:** could be as a result of:

- 1. Endocrine Disorder:** The ovaries and other endocrine organs communicate constantly. The interaction could explain how infertility manifests at various levels and make it challenging for the physician to diagnose infertility. If testing reveal a hypogonadotropic hypogonadism, a hypothalamic etiology of female infertility should be considered in the proper clinical setting. It might have physiological, functional, or organic roots. The implications of hyperprolactinemia on healthy gonadal function have been thoroughly studied, and effective treatments are available. Acromegaly and Cushing's illness both have different potential effects on fertility, but the underlying mechanisms are still poorly understood. Ovarian function can be directly affected by thyroid illnesses like hyperthyroidism and hypothyroidism, although autoimmune disease and changes in hormones levels may also be implicated (Abebe, Afework and Abaynew, 2020; Chemaitelly et al., 2021).
- 2. Specific Physical Conditions:** including excessive activity, anorexia nervosa, and obesity can all cause overweight or malnutrition, which can subsequently disrupt the menstrual cycle. Cause infertility (Unuane et al., 2011; Khetarpal and Singh, 2012; Akbaribazm, Goodarzi and Rahimi, 2021; Bendarska-Czerwińska et al., 2023; Silva et al., 2023).
- 3. Ovarian Disorders:** Due to elevated levels of LH and testosterone, diminish the uptake of glucose molecules by muscle, fatty molecules, and liver cells, polycystic ovarian disorder (PCO) can induce infertility and cause the pancreatic cells to produce and secrete a large amount of insulin hormone. Low levels of Follicle-Stimulating Hormone (FSH) can also plays a vital role

in preventing ovarian follicles from egg production, which can result in formation of cysts that are filled with fluid covers the ovaries and prevent the conception (Unuane et al., 2011; Khetarpal and Singh, 2012; Akbaribazm, Goodarzi and Rahimi, 2021; Bendarska-Czerwińska et al., 2023; Silva et al., 2023).

- 4. Endometriosis:** The literatures are replete with persuasive evidence that endometriosis negatively affects ovarian, tubal, and uterine receptivity and leads to female infertility. Endometriosis-related infertility is thought to be resulted by a variety of causes, including aberrant follicular development, increased oxidative stress, altered immunological response, changed hormonal milieu in the follicular and peritoneal environments, and decreased endometrial receptivity. Poor oocyte quality, compromised fertilization, and problematic implantation result from these conditions. Early studies stated that about 30% to 50% of patients with endometriosis suffer infertility and 25% of infertile women may have endometriosis problems. Endometriosis is more common in infertile women (48%) than it is in fertile women having tubal ligation (5%). Other studies have verified that infertile women are 6–8 times more likely than fertile women to have endometriosis (Surrey et al., 2002; Gupta et al., 2008; Botha and Kruger, 2014).

### **3.2.Second: Transport Problem**

- 1. Ovum Transport Failure:** Tubal obstruction can be brought on by Pelvic Inflammatory Disease (PID), gonorrhea, peritonitis, prior tubal surgery, and fimbrial adhesions. As a result, the egg is either retained or not released, which delays conception (Sumtsov, 2023).
- 2. Scar Tissue Following Abdominal Surgery:** Infertility may develop from abdominal procedures because scar tissue may affect how the ovaries, fallopian tubes, and uterus move (Niknejad, 2022).
- 3. Sperm Issues:** male infertility is referred to a man whose sperm characteristics are lower than that described by World Health Organization (WHO) stated levels. The most common causes of men infertility include abnormal sperm shape (teratospermia), low concentration (oligospermia), and poor motility (asthenospermia). About 90% of male infertility is related to the previous three causes. Other factors such as semen volume and other seminal markers of epididymal, prostatic, and seminal vesicle activity are other parameters less well associated with infertility. Pre-testicular, testicular, and post-testicular factors, as well as other regulatory mechanisms, can cause problems with number, motility, and morphology of sperms (Kumar and Singh, 2015; Jia, Wang and Yin, 2021; Saadh et al., 2023).
- 4. Cervix Problems:** Sperms migration from vagina to uterus might be quite challenging if cervical mucus changes in texture (Kumar and Singh, 2015; Jia, Wang and Yin, 2021; Saadh et al., 2023).

### **3.3.Third: Implantation Failure**

The implantation of the zygote and uterine fibroids near the fallopian tubes or cervix may be affected by congenital uterine anomalies such a bicornuate uterus result in infertility. In addition to the above causes, some scientists illustrate other causes that can result in infertility such as age, exposure to a specific type of chemicals which can affect the levels of hormones, smocking, alcohol drinking, and sexual transmitted diseases and genetic causes (Takeshima et al., 2021; Sengupta et al., 2022)

## **4. Pathophysiology of Infertility**

The main causes of infertility are explained above, the pathophysiology under this condition is differ according to the underlying cause as will explain below:

#### **4.1. Anovulation**

Ovulatory abnormalities account for about 25% of infertility causes. In this disorder there is no ovulation or oligo-ovulation which mean no release of oocyte for months period that is counter to normal condition. The presence of oocyte is considered the major condition for fertilization and pregnancy (Yatsenko and Rajkovic, 2019). Unhealthy lifestyle, unhealthy food, and extreme exercise are associated with functional hypothalamic amenorrhea (FHA), which is characterized by a reduction in the release of the GnRH hormone by the hypothalamus. The increased cortisol is created by the reduced calorie intake, related weight loss, or severe activity suppresses GnRH (Ackerman *et al.*, 2013). Gonadotropins, (FSH), and (LH) are released from the anterior pituitary gland less frequently when GnRH is pulsatile or not at all. Low estrogen levels, anovulation, and irregular follicle growth are resulted from these two deficiencies. Despite the levels of FSH and LH will vary between normal and low levels, the hormone ratio can reflect that of a pre-pubertal female, with FSH being higher than LH (Ackerman *et al.*, 2013; Yatsenko and Rajkovic, 2019). Infertility caused by PCOS is supposed to be a result of a fluctuation in follicle maturation which is finished with anovulation. Usually, Estrogen and FSH have normal ranges while LH may be normal or higher than normal levels. The etiology of PCOS and infertility is poorly known, although traditionally, aberrant GnRH pulsatility is described as a potential contributing factor. Anti-Mullerian hormone (AMH) increase and the high of stopped follicles and polycystic ovaries are related. Prolactin hormone interrupt and reduce the release of hypothalamic GnRH, which leads to lower LH levels and anovulation, oligomenorrhea, or amenorrhea. Progesterone is not released enough from the corpus luteum when prolactin serum levels between 20 and 50 ng/mL are present, shortening the luteal phase. Prolactinoma is known to be an etiology of luteal phase problems that cause infertility, while being debatable. Amenorrhea or oligomenorrhea is brought on by prolactin range between (50 and 100 ng/mL) because of aberrant feedback on the hypothalamic-pituitary-ovarian axis. High levels of more than 100 ng/mL is most frequently linked to pituitary adenomas and is related with overt hypogonadism and amenorrhea (Chen and Burt, 2017; Samperi, Lithgow and Karavitaki, 2019; Glezer and Bronstein, 2022).

#### **4.2. Endometriosis**

Endometrial tissue lining the uterine cavity is known as endometriosis. The presence of endometrial glands and/or stroma outside the uterus serves as the criteria for the diagnosis. Endometriosis affects 10 – 15 percent of women during their childbearing age and is usually affect the women pelvic area, however it can also see in the whole abdominal cavity. About fifty percent of women will suffer pregnancy problems if they are diagnosed with endometriosis and they faced difficulties to become pregnant (Parasar, Ozcan and Terry, 2017; Rolla, 2019; Lamceva, Uljanovs and Strumfa, 2023). The American Society of Reproductive Medicine names endometriosis into four stages, with stage one being mild and stage four being sever. Infertility is a commonly known end result of endometriosis; however, the pathophysiology is thought to be different depending on the stage of the disease (Johnson *et al.*, 2017; Rolla, 2019). In the first and second stages, infertility is assumed to be caused by inflammation, which is identified by greater level of prostaglandins, cytokines, macrophages, and Natural killer Cells (NKC). On other hands, follicular maturation, fertilization and implantation could be affected and failed by the presence of inflammation since it can cause defect of ovaries and tubal function. Pelvic adherence and appearance of masses can result in pelvic anatomical changes especially in stage 3 and 4 leading to prevention of oocyte release and sperm motility ended with infertility. Additionally, it is believed that advanced endometriosis hinders follicular-genesis, which lowers the likelihood of conception (Devroey, Fauser and Diedrich, 2009; Carson and Kallen, 2021).

### **4.3.Uterine Related Infertility**

The most prevalent tumor in women, uterine fibroids are almost typically benign that result in infertility. They also depend heavily on the ovarian steroids. They are thought to be monoclonal tumors, whose biological origin is unclear, it is developed from a mutation in a single myometrial somatic stem cell following numerous cycles of growth and involution under the influence of hormones (Freytag *et al.*, 2021), gynecological specialist also states that women who experience unexplained infertility have impaired peri-implantation endometrial perfusion which is clearly noted by Doppler examination (El-Mazny, Abou-Salem and Elshenoufy, 2013).

## **5. Types of Infertility**

Infertility is sub classified into two major types, primary and secondary as explained below (Davari Tanha, Mohseni and Ghajarzadeh, 2014; Mannonovna, 2022):

1. Primary infertility: Primary infertility characterized by that no pregnancy occur at all either because of age, genetic causes, or unknown causes.
2. Secondary infertility: in this type, the woman has at least one successful birth, this can occur as a result of disease such as uterine disorder as mention above, smocking, chemical exposure and other causes.

Both types of infertility are considered one of the most important negative events in society and can lead to a number of medical problems such as anxiety, headache, depression, and can affect over all couple life.

## **6. Diagnosis of Infertility**

The first step in the evaluation women with infertility is counseling and taken a medical history of the women such as infertility period, menstrual cycle type (regular, irregular), pregnancy information, contraceptive method if used, concurrent disease, medications, and family history. Then the following points should be evaluated to diagnose the cause of infertility:

### **6.1.First: Evaluation of The Female Endocrine System**

#### **6.1.1. Heat Measurement**

The easiest technique for assessing ovulation is Basal Body temperature (BBT). The temperature of the body increases by 0.5 to 1 degrees Fahrenheit during the second part of the menstrual cycle due to elevated progesterone levels. A BBT chart that shows an increase in temperature after days 11–16 for a period of 12–14 days is regarded as typical. It is revealed that ovulation occurs two days after or before continuous rise in body temperature in about 90% of women (Su *et al.*, 2017).

#### **6.1.2. Biopsy of Endometrium**

Gynecologic procedures including Endometrial Biopsies (EB) are commonly carried out in clinical settings. To execute an EB, a variety of tools and methods are available. In recent years, the requirement for diagnostic dilatation and curettage (D&C) or operational hysteroscopy, which are both typically carried out in the operating place with general anesthesia, has been replaced with office-based endometrial sampling (Vitale *et al.*, 2023).

#### **6.1.3. LH Urinary Level**

Within 1-2 days, the mid-cycle LH spike that precedes ovulation can be identified using several commercial "ovulation predictor kits" that measure urinary luteinizing hormone (LH). The indirect indicator of ovulation is the finding of LH in the urine. When the test is run on midday or evening urine samples, results often correlate well with the peak in serum LH. Patients with PCOS may experience tonic elevations in basal LH levels, which can cause urine LH levels to test falsely positive. Testing,

however, can provide false-positive and false-negative results, and accuracy, usability, and reliability differ among products (Pfeifer *et al.*, 2017; Penzias *et al.*, 2021; ‘Optimizing natural fertility: a committee opinion’, 2022).

#### **6.1.4. Ultrasonography**

It is a highly helpful clinical tool for assessing follicular development and ovulation and can be carried out either abdominally or, preferable, trans-vaginally. Follicles typically mature and burst between sizes: 17 to 22 mm. Ovulation is indicated by the diminution of follicular size, the disappearance of transparent follicles, and the presence of fluid in the cul-de-sac. A sign of PCO is the appearance of numerous tiny follicles. Additionally, endometrial thickness greater than 8 mm during the mid-luteal phase indicates that the post-ovulatory endometrium is normally formed. The capacity of pelvic ultrasonography (US, including sonohysterography and contrast-enhanced hysterosalpingosonography), hysterosalpingography (HSG), and magnetic resonance imaging (MRI) of the female reproductive system is highlighted as additional information that imaging studies can provide to reproductive medicine (Dishuck *et al.*, 2019).

#### **6.1.5. FSH and Estradiol 2 (E2) Measurement**

The upper normal levels for this test (FSH) is typically 10–13 mIU/ ml. Results lower this range are considered normal, but levels near to 20 mIU/ml usually connected to significantly reduced pregnancy rates. To avoid an incorrect interpretation of the test results, E2 is nearly typically examined concurrently with the FSH level. Studies have shown that merely one increased cycle day 2-4 FSH level is linked to a worse outcome (Kumar and Sait, 2011).

#### **6.1.6. Laparoscopy**

Laparoscopy has developed over the past few years into a potent prophylactic and therapeutic tool in contemporary gynecological therapy. With very low complication rates, it can decrease the number of inappropriate operations and wasteful treatments<sup>5–9</sup>. When used in conjunction with other propaedeutic procedures, laparoscopy has a greater ability to diagnose diseases than prior clinical and ultrasound tests, which could alter the diagnosis in many gynecological cases (Argentino *et al.*, 2019).

### **6.2.Second: Pelvic Factors Examination**

#### **6.2.1. Hysteroscopy**

Tubal catheterization is an operation used to clear blocked tubes and see the inside of the tubes. It can be used as a therapeutic mean or diagnostic tool. Finding out how well the fallopian tubes are functioning may be possible thanks to this diagnostic procedure. Adhesions and probable surgical and anesthesia problems are disadvantages of the surgery. Due to the lack of data on the role of hysteroscopic surgical procedure in sub-fertile women with polyps, fibroids, a septate or bipartite uterus, or intrauterine adhesions, Randomized Control Trials (RCTs) are advised to be conducted (Bosteels *et al.*, 2009).

#### **6.2.2. Magnetic Resonance Imaging (MRI)**

This technique is characterized by accurate and confident results that make it helpful in diagnosis of complex cases that cannot be diagnosed by other methods. But, because of its high cost, patients do not use it frequently.

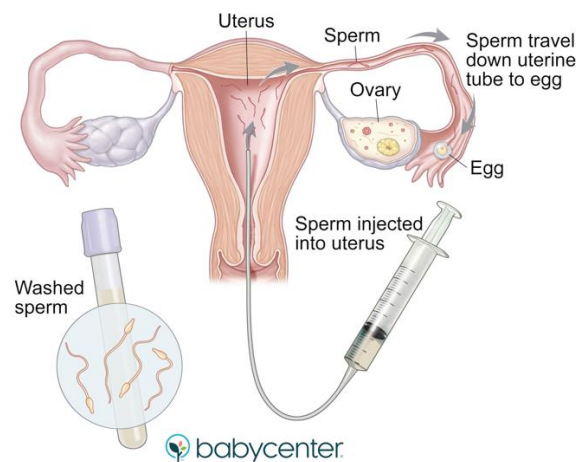
### **6.3.Third: Cervical Assessment**

This includes post-coital test to take information about sperm counting, mucus thickness and others, anti-sperm antibody (in specific type of patient), and cervical culture to investigate the type of bacterial or other infections that may contribute to the infertility (Campisciano *et al.*, 2017).

## 7. Treatment of Infertility

Treatment of infertility is largely depending on the cause of the condition. For example, if the obesity is the underlying cause so the women should be advised to reduce her weight and taken healthy food. If the smoking was the cause, it should be stopped. Therefore, the accurate diagnosis is important to achieve the desired target. In some cases, infection could be the primary cause of fertility failure like *E. coli* and chlamydia species. In such case, appropriate antimicrobial regimen should be used to eradicate the causative agents. It should be mentioned that some of infertility causes cannot be corrected and that should be explained for the couples, and they should know the details of any method that will be carried out for them (Bosteels *et al.*, 2009; Kumar and Sait, 2011; Campisciano *et al.*, 2017). In some cases when the infertility cause is not identified (idiopathic infertility) one of the following strategies could be beneficial to produce successful pregnancy:

1. **Intra-Uterine Insemination (IUI):** For couples who are experiencing unexplained subfertility, mild endometriosis or male source infertility, intrauterine insemination (IUI) is a common technique for fertility treatment. IUI is less invasive and more affordable than in vitro fertilization (IVF), although there is controversy over whether IUI combined with ovarian hyperstimulation (OH) is safe. The rise in multiple pregnancy rates is the main issue with IUI treatment with OH as shown in Fig.3 (Sicchieri *et al.*, 2018; Turan, 2023).



**Figure 3:** Intrauterine Insemination (IUI) (Turan, 2023)

2. **In-Vitro Fertilization:** This technique involves stimulation of women ovaries by using appropriate pharmacological courses, then the eggs are taken outside women body in special sterilized conditions and fertilized with sperm that taken from the husband. The fertilized eggs cultured and then the embryo is retaining to mother inside her uterus. This process is usually used in couples with male- related problems. This technique is used know largely in IVF centers. As the exact causes of the hazards of IVF to child health are unknown, IVF therapy should only be used in situations of infertility that cannot be cured by any other methods in order for the children to be created (Asplund, 2020; Ferrell, Choudhry and Schon, 2024). The ovaries are stimulated by daily injections of gonadotropins to optimize follicular development, which is monitored by means of transvaginal ultrasonography. Ultrasonography of an unstimulated ovary shows a small antral follicle (Panel A, arrow). The same ovary has multiple growing follicles after gonadotropin stimulation. One follicle is shown with measurements in two dimensions (Panel B). After ovarian stimulation, eggs are retrieved by means of ultrasound-guided transvaginal aspiration of

follicular fluid (Panel C). A mature human egg is recovered from the aspirated fluid (Panel D). Recovered eggs are often fertilized in vitro by culturing eggs with many motile sperm (Panel E); in this image, multiple sperm are attached to the egg's zona pellucida (arrows point to three of the sperm) (Asplund, 2020; Simon, Rajendra Kumar and Duncan, 2020; Jirge et al., 2022). Eggs can also be fertilized by means of intracytoplasmic sperm injection, a technique in which a single sperm is injected into the egg with the use of a thin glass pipette (Panel F). This technique was developed to facilitate fertilization in cases of male-factor infertility but is now used in a majority of IVF cycles. Multiple embryos are cultured, often for 3 days (an eight-cell embryo, shown in Panel G) or 5 days (a blastocyst embryo, shown in Panel H, with the inner cell mass indicated by the arrow) before selected embryos are transferred back to the uterus (Panel I). Good-quality, excess embryos are often cryopreserved (Asplund, 2020; Turan, 2023; Ferrell, Choudhry and Schon, 2024).

### **3. Zygote Intra-Fallopian Transfer (ZIFT) And Gamete Intrafallopian Transfer Technique (GIFT).**

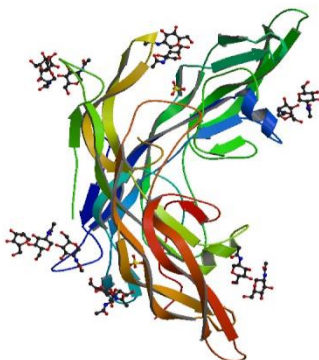
In Texas in 1984, Ricardo Asch carried out the first successful gamete intra-fallopian transfer (GIFT). According to the theory, the GIFT operation most closely resembles the process of natural fertilization and is therefore approved by the Vatican. This makes it possible to do in-vivo fertilization without manipulating or discarding the embryos. To maximize each parent's contribution, ovarian stimulation is started in the female partner when patency has been established, and sperm activation in the male spouse. The eggs are transvaginally collected after they are fully developed. They are then put into a specialized catheter and laparoscopically inserted into the tube via the fimbrial end of the fallopian tube along with the capacitated sperm. The next step is fertilization, which results in timely implantation into the uterus and the onset of a healthy pregnancy (Thurmond, 2013; Hong *et al.*, 2023). Infertility caused by some ovarian and cervical disorders, minor endometriosis, adhesions treatable with surgical endoscopy, and unsuccessful IUI are all conditions that can be treated with GIFT. Additionally, it has been demonstrated in some Millerian situations to be effective (Lee and Lie, 2012). Later, in 1986, Zygote was used to treat a patient with anti-sperm antibodies (as Intra-Fallopian Transfer (ZIFT)). Then it was called Tubal Embryo Transfer (TET). Cases of its use include severe male factor infertility and anti-sperm and RIF (repeated implantation failure). The process is similar to GIFT, but instead of inserting gametes, a zygote is transferred after one day after laboratory fertilization. A sperm must enter an egg and fuse with it in order for a zygote to develop (Lee and Lie, 2012; Thurmond, 2013)

- 4. Assisted Hatching:** A procedure called assisted hatching is occasionally employed in assisted reproduction for intracytoplasmic sperm injection (ICSI) and in vitro fertilization (IVF). It entails opening a hole in the fertilized egg or weakening the covering around it. It is hypothesized that doing so would increase the embryo's likelihood of fusing to the womb's lining and initiating a pregnancy (Carney *et al.*, 2012; Lacey *et al.*, 2021).
- 5. Donor Eggs and Sperms:** The eggs and sperm used in assisted reproduction technologies are typically those of the married couple, however in cases where there are serious problems with the eggs and sperm, donor sperm or even embryos may be used to increase fertility (Anwar and Anwar, 2016; Shahnaz and Ayesha, 2016).
- 6. Medications:** To induce ovulation, fertility medications are frequently used as a sole form of treatment. If the use of such medications is failed or no enough response, they may be joined with other reproductive technologies, such as in-vitro fertilizations. The American Society for Reproductive Medicine categorizes fertility medications into three groups (Carney *et al.*, 2012; Anwar and Anwar, 2016; Shahnaz and Ayesha, 2016; Lacey *et al.*, 2021):

- A. Ovarian Stimulation Medications.** Human menopausal gonadotrophin (hMG) [e.g. Humegon]; follicle-stimulating hormone (FSH) [e.g. Follistim]; luteneizing hormone (LH) [e.g. Luveris]; clomiphene (e.g. Clomid); and letrozole (Femara).
- B. Oocyte Maturation Medications.** hCG [Profasi, APL, Pregnyl, Novarel, Ovidrel] is a human chorionic gonadotropin.
- C. Drugs That Stop Premature Ovulation.** Lupron and Synarel are GnRh agonists; Antagon and Cetrotide are GnRH antagonists.

## 8. Follitropin

It is a medicine that mimic in its activity to the Follicle- Stimulating Hormone that is produced by recombinant DNA technology. Follitropin has two non-identical glycoprotein called alfa and beta with chemical structure shown in Fig.4. FSH is produced by pituitary gland and have the same activity in eggs development process. Follitropin is used as subcutaneously injection to induce fertility in female who have infertility issues as well as in male to induce sperm synthesis and maturation (Thurmond, 2013).



**Figure 4:** Chemical Structure of Follitropin (Thurmond, 2013)

### 8.1. Pharmacodynamic

Follitropin is recombinant form of endogeneous FSH (synthesized in china by using laboratory hamster), follitropin bind to the same receptor of FSH which is G-protein coupled transmembrane type. The binding of substrate to the receptor induce a phosphorelation and activation the enzyme Phosphatidylinositol-3-kinase and AKt signaling pathway. Follitropin have tow subunits (alpha and beta). Many metabolic, survival, and maturation of cells function are depending on this pathway activation. For these actions, it could be used for patients with secondary infertility that is respond to other therapies (Schwarze *et al.*, 2022).

### 8.2. Pharmacokinetic

Follitropin alpha's pharmacokinetics are similar to those of the hormone produced by the body. A 2-compartment model with first-order absorption is used to characterize the pharmacokinetics of follitropin alpha after subcutaneous delivery to healthy female volunteers who had been given the GnRH agonist goserelin as pituitary down-regulation. In 4 days, steady state is attained (Abd-Elaziz *et al.*, 2017; Manzi *et al.*, 2022). Mean peak plasma concentrations are three times larger at steady state than they are after a first single dosage, and the volume of distribution is comparable to extracellular water. Following the delivery of follitropin alpha, serum FSH levels do not correlate with pharmacodynamic or clinical effects and are not helpful

in predicting or monitoring the success of treatment. Endogenous FSH is excreted by the kidneys and liver. Follitropin alpha's terminal elimination half-life values vary among people by up to 70% (Abd-Elaziz et al., 2017; Manzi et al., 2022; Schwarze et al., 2022).

### **8.3. Medical Uses**

This drug, which treats some female fertility issues, contains follicle-stimulating hormone (FSH). To encourage healthy ovaries to generate eggs, follitropin alfa is used. Typically, this medicine is used with another hormone (hCG) to cause the development and release of a mature egg (ovulation). Women with primary ovarian failure, in which the ovaries are unable to produce eggs, are not advised to take this drug (Christen et al., 2011).

### **8.4. Side Effects**

Allergic reactions, ovarian hyper-stimulation, weight gain, nausea, loss of appetite, sweating and vomiting are the most common side effects associated with the use of alpha follitropin. But it's used is consider safe in most cases because not all drawbacks could be occurred to the patient (Schertz et al., 2011; Prasetiawati et al., 2023).

### **8.5. Caution and Contraindications**

It is not advised for pregnant women to use follitropin alfa, which is used to induce ovulation. Multiple births, spontaneous abortion, ectopic pregnancies, and congenital anomalies have all been contraindicated (Christen et al., 2011; Prasetiawati et al., 2023).

## **9. Clomiphene Citrate**

Clomiphene (Clomid<sup>®</sup>) is one of the most commonly medicine used by Gynecologist to treat infertility caused by anovulation or oligo-ovulation especially female with polycystic ovarian syndrome since it is considered the first line therapy in such patients. It is non-steroidal compound available as 50mg oral tablets. It is used from fifth day to ninth day of menstrual cycle. Clomiphene acts by increasing the follicle stimulating hormone (FSH) by blocking the receptors of estrogen resulting in development of greater number of eggs that can fertilized and pregnancy occurrence. The most common side effect of clomiphene includes ovaries enlargement but this is not common, abnormal vaginal bleeding were recorded, gastrointestinal discomfort (nausea, vomiting, and bloating), hot flashes, headache, and visual problems. Instead of that, clomiphene is well tolerated by patients and therapeutic monitoring by ultrasound is important to evaluate its effects. On other hands, huge number of studies stated the importance of used clomiphene in infertile men, since it helps in induce spermatogenesis. Finally, clomiphene is metabolized by the liver and excreted with stool (Hughes et al., 2000, 2010; Homburg, 2005; Yilmaz et al., 2018).

## **10. Lerozole**

Lerozole firstly tested in 1986 by Giba-Geigy in vivo and was used for breast cancer which was first and only registered use. It is nonsteroidal third generation aromatase inhibitors that prevent estrogen synthesis by interfering with its first limiting step (reversibly prevent P450 enzyme aromatase) in estrogen biosynthesis. Also, it prevents estradiol and estrogen formation. With time, further animal and clinical studies were performed and revealed that lerozole have great effect in increasing ovulation especially in women with polycystic ovarian syndrome even more than Clomiphene. It could be used alone or as adjuvant agent with Intra Uterine Insemination. Hot flashes and abdominal pain and cramps were reported with short treatment course. While when used for long period such as for breast cancer more serious side effect where reported such as Malaysia and arthralgia

after five years treatment period. It is metabolized in the liver by CYP450 3A4 and 2A6 and excreted in urine with half-life of two days (Yang et al., 2021; Pajai et al., 2022).

### **11. Leuprorelin**

Leuproreline is a gonadotropin releasing hormone agonist that enhance synthesis and secretion of LH and FSH from anterior pituitary gland resulting in suppression of circulating sex hormones. therefore, it used in some disease with hormonal deterioration such as prostate cancer, endometriosis, and precocious puberty. Long duration use of Leuprorelin cause desensitization of pituitary gland or down regulation there for its used is limited for short courses (not more than 6 months). Leuprorelin is peptide compound that cannot be used orally. Subcutaneous and intramuscular sustain release injection form are available (3.75mg and 7.5mg depot injection) are used monthly or as prescribed by physician to prevent local side effects. Sweating, hot flashes, swelling, headache, weakness, fatigue, and sexual side effects are the most common recorded side effects (Sanfilippo and Sethi, 2009; Sethi and Sanfilippo, 2009).

### **12. Metformin**

Metformin is a biguanide hypoglycemic agent. Its main use in type-2 diabetes mellitus. It is insulin sensitizer agent that reduce insulin resistance and improve glucose metabolism. Recent studies revealed the role of metformin in reducing insulin resistance that caused by polycystic ovarian syndrome and cause hyperandrogenism, anovulation and other reproductive system problems. International guidelines for treatment of PCOS stated that metformin could be used with lifestyle modification or with other contraceptive pills for obese patient and non-obese patient could use it also. It could also be used in adolescent with BMI  $\geq 25$  kg/m<sup>2</sup> for weight and hormonal disturbances. It is well tolerated drug and not cause hypoglycemia. Metformin is well tolerated and available orally tablets with low cost , the most common side effects of metformin include gastrointestinal discomfort and deficiency of vitamin B12 and folic acid with long term use. These side effects could be reduced by taken the drug with meals or taken as supplements (Magzoub et al., 2022).

### **13. Gonadotropin- Releasing Hormone Analogues**

A group of drugs act by enhancing the secretion of LH and FSH from the pituitary gland. It is usually used for infertile women who are not ovulate or have problems in their ovulation process and menstrual cycle. In addition, these agent could be used for infertile men also. To give maximum effect, these agents usually used with other fertility intervention such as IUI and IVF. Continuous used of these agents can result in suppression of gonadotropin hormone production and release. These agents include (Buserelin, Gonadorelin, Goserelin, Histrelin, Leuprorelin, Nafarelin, and Triptorelin).

The administration of these compound started with the menstrual cycle to enhance ovulation and follicular maturation. Because this type of drug cause decrease in Oestrogen levels, the main side effect is similar to that of menopause which include hot flashes, moon changes, dryness of vagina, and osteoporosis risk is increased. Finally, these agents are synthesized as small peptide there for they given as injection formula but not oral (Flanagan and Manilall, 2017; Goodman et al., 2022; Resta et al., 2023).

### **14. Conclusion**

Infertility is a pathological condition known by inability to become conceive after twelve months of non-protected intercourse. Both men and women can have infertility and the majority of these conditions are treatable. The primary cause of women infertility is anovulation, transport problem, and tubular defects. With time, development of new intervention and production of new active medicines lead to reduce the effect of such problem to the couples.

## 15. Conflict of Interest

Authors declare no conflict of interest

## References

- Abd-Elaziz, K. *et al.* (2017) 'A new fully human recombinant FSH (follitropin epsilon): Two phase i randomized placebo and comparator-controlled pharmacokinetic and pharmacodynamic trials', *Human Reproduction*, 32(8). Available at: <https://doi.org/10.1093/humrep/dex220>.
- Abdullah, A.A., Ahmed, M. and Oladokun, A. (2021) 'Prevalence of infertility in Sudan: A systematic review and meta-analysis', *Qatar Medical Journal*, 2021(3). Available at: <https://doi.org/10.5339/qmj.2021.47>.
- Abebe, M.S., Afework, M. and Abaynew, Y. (2020) 'Primary and secondary infertility in Africa: systematic review with meta-analysis', *Fertility Research and Practice*, 6(1). Available at: <https://doi.org/10.1186/s40738-020-00090-3>.
- Ackerman, K.E. *et al.* (2013) 'Cortisol secretory parameters in young exercisers in relation to LH secretion and bone parameters', *Clinical Endocrinology*, 78(1). Available at: <https://doi.org/10.1111/j.1365-2265.2012.04458.x>.
- Agbana, R.D., Michael, T.O. and Ojo, T.F. (2023) 'Family planning method discontinuation among Nigerian women: Evidence from the Nigeria Demographic and Health Survey 2018', *Journal of Taibah University Medical Sciences*, 18(1). Available at: <https://doi.org/10.1016/j.jtumed.2022.08.003>.
- Akbaribazm, M., Goodarzi, N. and Rahimi, M. (2021) 'Female infertility and herbal medicine: An overview of the new findings', *Food Science and Nutrition*. Available at: <https://doi.org/10.1002/fsn3.2523>.
- Al-Kareem, M.A. *et al.* (2022) 'Measurement the Self-efficacy Among Infertile Women in Al-Hilla City, Iraq', *Iranian Rehabilitation Journal*, 20(1). Available at: <https://doi.org/10.32598/irj.20.1.1621.2>.
- Anwar, S. and Anwar, A. (2016) 'Infertility: A Review on Causes, Treatment and Management', *Womens Health & Gynecol*, 2(6).
- Argentino, G.L.S. *et al.* (2019) 'The role of laparoscopy in the propaedeutics of gynecological diagnosis', *Acta Cirurgica Brasileira*, 34(1). Available at: <https://doi.org/10.1590/s0102-865020190010000010>.
- Asplund, K. (2020) 'Use of in vitro fertilization—ethical issues', *Upsala Journal of Medical Sciences*. Available at: <https://doi.org/10.1080/03009734.2019.1684405>.
- Bayoumi, R.R. *et al.* (2021) 'Quality of life of Sudanese patients attending a fertility clinic: a mixed methods study', *Health Psychology and Behavioral Medicine*, 9(1). Available at: <https://doi.org/10.1080/21642850.2021.2007773>.
- Bendarska-Czerwińska, A. *et al.* (2023) 'Endocrine disorders and fertility and pregnancy: An update', *Frontiers in Endocrinology*. Available at: <https://doi.org/10.3389/fendo.2022.970439>.
- Bosch, E. *et al.* (2021) 'Reduced FSH and LH action: Implications for medically assisted reproduction', *Human Reproduction*. Available at: <https://doi.org/10.1093/humrep/deab065>.
- Bosteels, J. *et al.* (2009) 'The effectiveness of hysteroscopy in improving pregnancy rates in subfertile women without other gynaecological symptoms: A systematic review', *Human Reproduction Update*. Available at: <https://doi.org/10.1093/humupd/dmp033>.
- Botha, D.J. and Kruger, T.F. (2014) 'Pathogenic mechanisms in endometriosis associated infertility', *Obstetrics and Gynaecology Forum*.
- Campisciano, G. *et al.* (2017) 'Subclinical alteration of the cervical–vaginal microbiome in women with idiopathic infertility', *Journal of Cellular Physiology*, 232(7). Available at: <https://doi.org/10.1002/jcp.25806>.

- Carney, S.K. *et al.* (2012) 'Assisted hatching on assisted conception (in vitro fertilisation (IVF) and intracytoplasmic sperm injection (ICSI)', *Cochrane Database of Systematic Reviews*. Available at: <https://doi.org/10.1002/14651858.CD001894.pub5>.
- Carson, S.A. and Kallen, A.N. (2021) 'Diagnosis and Management of Infertility: A Review', *JAMA - Journal of the American Medical Association*. Available at: <https://doi.org/10.1001/jama.2021.4788>.
- Chemaitelly, H. *et al.* (2021) 'Global epidemiology of Neisseria gonorrhoeae in infertile populations: Systematic review, meta-analysis and metaregression', *Sexually Transmitted Infections*, 97(2). Available at: <https://doi.org/10.1136/sextrans-2020-054515>.
- Chen, A.X. and Burt, M.G. (2017) 'Hyperprolactinaemia', *Australian Prescriber*, 40(6). Available at: <https://doi.org/10.18773/austprescr.2017.060>.
- Christen, M. *et al.* (2011) 'The redesigned follitropin  $\alpha$  pen injector for infertility treatment', *Expert Opinion on Drug Delivery*, 8(6). Available at: <https://doi.org/10.1517/17425247.2011.581658>.
- Davari Tanha, F., Mohseni, M. and Ghajarzadeh, M. (2014) 'Sexual function in women with primary and secondary infertility in comparison with controls', *International Journal of Impotence Research*, 26(4). Available at: <https://doi.org/10.1038/ijir.2013.51>.
- Devroey, P., Fauser, B.C.J.M. and Diedrich, K. (2009) 'Approaches to improve the diagnosis and management of infertility', *Human Reproduction Update*, 15(4). Available at: <https://doi.org/10.1093/humupd/dmp012>.
- Dishuck, C.F. *et al.* (2019) 'Advanced Imaging in Female Infertility', *Current Urology Reports*. Available at: <https://doi.org/10.1007/s11934-019-0942-0>.
- El-Mazny, A., Abou-Salem, N. and Elshenoufy, H. (2013) 'Doppler study of uterine hemodynamics in women with unexplained infertility', *European Journal of Obstetrics and Gynecology and Reproductive Biology*, 171(1). Available at: <https://doi.org/10.1016/j.ejogrb.2013.08.026>.
- Ferrell, E.L., Choudhry, A.A. and Schon, S.B. (2024) 'Obesity and in Vitro Fertilization', *Seminars in Reproductive Medicine*, 41(3–4). Available at: <https://doi.org/10.1055/s-0043-1776420>.
- Flanagan, C.A. and Manilall, A. (2017) 'Gonadotropin-releasing hormone (GnRH) receptor structure and GnRH binding', *Frontiers in Endocrinology*, 8(OCT). Available at: <https://doi.org/10.3389/fendo.2017.00274>.
- Freytag, D. *et al.* (2021) 'Uterine fibroids and infertility', *Diagnostics*. Available at: <https://doi.org/10.3390/diagnostics11081455>.
- Glezer, A. and Bronstein, M.D. (2022) 'Hyperprolactinemia', in *Endocrinology and Diabetes: A Problem Oriented Approach: Second Edition*. Available at: [https://doi.org/10.1007/978-3-030-90684-9\\_5](https://doi.org/10.1007/978-3-030-90684-9_5).
- Goodman, R.L. *et al.* (2022) 'Neuroendocrine control of gonadotropin-releasing hormone: Pulsatile and surge modes of secretion', *Journal of Neuroendocrinology*. Available at: <https://doi.org/10.1111/jne.13094>.
- Gupta, S. *et al.* (2008) 'Pathogenic mechanisms in endometriosis-associated infertility', *Fertility and Sterility*. Available at: <https://doi.org/10.1016/j.fertnstert.2008.02.093>.
- Homburg, R. (2005) 'Clomiphene citrate - End of an era? A mini-review', *Human Reproduction*. Available at: <https://doi.org/10.1093/humrep/dei042>.
- Hong, P. *et al.* (2023) 'Impact of Endometriosis on the Therapeutic Effect of Hysteroscopic Fallopian Tube Catheterization Combined with Laparoscopy in Infertile Patients with Proximal Tubal Obstruction', *Journal of Sichuan University (Medical Science)*, 54(5). Available at: <https://doi.org/10.12182/20230960205>.

- Hughes, E. *et al.* (2000) 'Clomiphene citrate for unexplained subfertility in women', in *Cochrane Database of Systematic Reviews*. Available at: <https://doi.org/10.1002/14651858.cd000057>.
- Hughes, E. *et al.* (2010) 'Clomiphene citrate for unexplained subfertility in women', *Cochrane Database of Systematic Reviews* [Preprint]. Available at: <https://doi.org/10.1002/14651858.cd000057.pub2>.
- Jia, W., Wang, C. and Yin, Y. (2021) 'Acupuncture for oligospermia and asthenozoospermia: A systematic review and meta-analysis', *Medicine (United States)*. Available at: <https://doi.org/10.1097/MD.00000000000027816>.
- Jirge, P.R. *et al.* (2022) 'Ovarian stimulation in assisted reproductive technology cycles for varied patient profiles: An Indian perspective', *Journal of Human Reproductive Sciences*. Available at: [https://doi.org/10.4103/jhrs.jhrs\\_59\\_22](https://doi.org/10.4103/jhrs.jhrs_59_22).
- Johnson, N.P. *et al.* (2017) 'World endometriosis society consensus on the classification of endometriosis', *Human Reproduction*, 32(2). Available at: <https://doi.org/10.1093/humrep/dew293>.
- Khetarpal, A. and Singh, S. (2012) 'Infertility: Why can't we classify this inability as disability?', *Australasian Medical Journal*. Available at: <https://doi.org/10.4066/AMJ.2012.1290>.
- Kumar, N. and Singh, A. (2015) 'Trends of male factor infertility, an important cause of infertility: A review of literature', *Journal of Human Reproductive Sciences*. Available at: <https://doi.org/10.4103/0974-1208.170370>.
- Kumar, P. and Sait, S. (2011) 'Luteinizing hormone and its dilemma in ovulation induction', *Journal of Human Reproductive Sciences*. Available at: <https://doi.org/10.4103/0974-1208.82351>.
- Lacey, L. *et al.* (2021) 'Assisted hatching on assisted conception (in vitro fertilisation (IVF) and intracytoplasmic sperm injection (ICSI))', *Cochrane Database of Systematic Reviews*, 2021(3). Available at: <https://doi.org/10.1002/14651858.CD001894.pub6>.
- Lamceva, J., Uljanovs, R. and Strumfa, I. (2023) 'The Main Theories on the Pathogenesis of Endometriosis', *International Journal of Molecular Sciences*. Available at: <https://doi.org/10.3390/ijms24054254>.
- Lee, C.S.S. and Lie, A.T.M. (2012) 'Successful pregnancy outcome following gamete intra-Fallopian transfer in a patient with Müllerian dysgenesis', *Reproductive BioMedicine Online*, 24(5). Available at: <https://doi.org/10.1016/j.rbmo.2012.01.021>.
- Magzoub, R. *et al.* (2022) 'Does metformin improve reproduction outcomes for non-obese, infertile women with polycystic ovary syndrome? Meta-analysis and systematic review', *European Journal of Obstetrics and Gynecology and Reproductive Biology*. Available at: <https://doi.org/10.1016/j.ejogrb.2022.01.025>.
- Mannonovna, R.M. (2022) 'Infertility in Women - Classification, Symptoms, Causes and Factors, Recommendations for Women', *Science and Innovation International Scientific Journal*, 1(7).
- Manzi, L. *et al.* (2022) 'Comparative Assessment of the Structural Features of Originator Recombinant Human Follitropin Alfa Versus Recombinant Human Follitropin Alfa Biosimilar Preparations Approved in Non-European Regions', *International Journal of Molecular Sciences*, 23(12). Available at: <https://doi.org/10.3390/ijms23126762>.
- Niknejad, M. (2022) 'Blocked fallopian tube', in *Radiopaedia.org*. Available at: <https://doi.org/10.53347/rid-147874>.
- Okonofua, F. *et al.* (1997) 'The social meaning of infertility in Southwest Nigeria', *Health Transition Review*, 7(930).
- 'Optimizing natural fertility: a committee opinion' (2022) *Fertility and Sterility*, 117(1). Available at: <https://doi.org/10.1016/j.fertnstert.2021.10.007>.
- Pajai, S. *et al.* (2022) 'A Review on the Use of Letrozole in Female and Male Infertility', *Cureus* [Preprint]. Available at: <https://doi.org/10.7759/cureus.31291>.

- Parasar, P., Ozcan, P. and Terry, K.L. (2017) 'Endometriosis: Epidemiology, Diagnosis and Clinical Management', *Current Obstetrics and Gynecology Reports*, 6(1). Available at: <https://doi.org/10.1007/s13669-017-0187-1>.
- Penzias, A. *et al.* (2021) 'Fertility evaluation of infertile women: a committee opinion', *Fertility and Sterility*, 116(5). Available at: <https://doi.org/10.1016/j.fertnstert.2021.08.038>.
- Pfeifer, S. *et al.* (2017) 'Optimizing natural fertility: a committee opinion', *Fertility and Sterility*, 107(1). Available at: <https://doi.org/10.1016/j.fertnstert.2016.09.029>.
- Prasetiawati, N. *et al.* (2023) 'The Effect of Follitropin Alfa in Controlled Ovarian Stimulation Protocol for In Vitro Fertilization Cycles', *Journal of Reproduction and Infertility*, 24(2). Available at: <https://doi.org/10.18502/jri.v24i2.12499>.
- Resta, C. *et al.* (2023) 'Gonadotropin-Releasing Hormone (GnRH)/GnRH Receptors and Their Role in the Treatment of Endometriosis', *Cureus* [Preprint]. Available at: <https://doi.org/10.7759/cureus.38136>.
- Rolla, E. (2019) 'Endometriosis: Advances and controversies in classification, pathogenesis, diagnosis, and treatment:.', *F1000Research*. Available at: <https://doi.org/10.12688/f1000research.14817.1>.
- Saadh, M.J. *et al.* (2023) 'Reduced expression of miR-221 is associated with the pro-apoptotic pathways in spermatozoa of oligospermia men', *Journal of Reproductive Immunology*, 160. Available at: <https://doi.org/10.1016/j.jri.2023.104159>.
- Samperi, I., Lithgow, K. and Karavitaki, N. (2019) 'Hyperprolactinaemia', *Journal of Clinical Medicine*. Available at: <https://doi.org/10.3390/jcm8122203>.
- Sanfilippo, N. and Sethi (2009) 'Six-month depot formulation of leuprorelin acetate in the treatment of prostate cancer', *Clinical Interventions in Aging* [Preprint]. Available at: <https://doi.org/10.2147/cia.s4885>.
- Schertz, J.C. *et al.* (2011) 'The redesigned follitropin alfa pen injector: Results of the patient and nurse human factors usability testing', *Expert Opinion on Drug Delivery*, 8(9). Available at: <https://doi.org/10.1517/17425247.2011.608350>.
- Schwarze, J.E. *et al.* (2022) 'Originator recombinant human follitropin alfa versus recombinant human follitropin alfa biosimilars in Spain: A cost-effectiveness analysis of assisted reproductive technology related to fresh embryo transfers', *Best Practice and Research: Clinical Obstetrics and Gynaecology*. Available at: <https://doi.org/10.1016/j.bpobgyn.2022.01.011>.
- Sengupta, P. *et al.* (2022) 'Endocrinopathies and male infertility', *Life*. Available at: <https://doi.org/10.3390/life12010010>.
- Sethi, R. and Sanfilippo, N. (2009) 'Six-month depot formulation of leuprorelin acetate in the treatment of prostate cancer.', *Clinical interventions in aging*.
- Sezgin, H., Hocaoglu, C. and Guvendag-Guven, E.S. (2016) 'Disability, psychiatric symptoms, and quality of life in infertile women: a cross-sectional study in Turkey', *Shanghai Archives of Psychiatry*, 28(2). Available at: <https://doi.org/10.11919/j.issn.1002-0829.216014>.
- Shahnaz and Ayesha (2016) 'Infertility: A Review on Causes, Treatment and Management', *Womens Health & Gynecol*, 2(6).
- Sharifi, F., Azizi, H. and Roudsari, R.L. (2022) 'Prevalence of complementary and alternative medicine use by Iranian infertile women: A multi-center cross-sectional study', *Journal of Herbal Medicine*, 32. Available at: <https://doi.org/10.1016/j.hermed.2022.100548>.
- Sicchieri, F. *et al.* (2018) 'Prognostic factors in intrauterine insemination cycles', *Jornal Brasileiro de Reproducao Assistida*, 22(1). Available at: <https://doi.org/10.5935/1518-0557.20180002>.
- Silva, A.B.P. *et al.* (2023) 'The role of endocrine disruptors in female infertility', *Molecular Biology Reports*. Available at: <https://doi.org/10.1007/s11033-023-08583-2>.

- Simon, L.E., Rajendra Kumar, T. and Duncan, F.E. (2020) 'In vitro ovarian follicle growth: A comprehensive analysis of key protocol variables', *Biology of Reproduction*. Available at: <https://doi.org/10.1093/biolre/ioaa073>.
- Su, H. *et al.* (2017) 'Detection of ovulation, a review of currently available methods', *Bioengineering & Translational Medicine*, 2(3). Available at: <https://doi.org/10.1002/btm2.10058>.
- Sumtsov, D. (2023) 'PRIMARY FALLOPIAN TUBE CANCER: A LITERATURE REVIEW', *Eastern Ukrainian Medical Journal*, 11(3). Available at: [https://doi.org/10.21272/eumj.2023;11\(3\):224-231](https://doi.org/10.21272/eumj.2023;11(3):224-231).
- Surrey, E.S. *et al.* (2002) 'Effect of prolonged gonadotropin-releasing hormone agonist therapy on the outcome of in vitro fertilization-embryo transfer in patients with endometriosis', in *Fertility and Sterility*. Available at: [https://doi.org/10.1016/S0015-0282\(02\)03373-3](https://doi.org/10.1016/S0015-0282(02)03373-3).
- Tabong, P.T.N. and Adongo, P.B. (2013) 'Infertility and childlessness: A qualitative study of the experiences of infertile couples in Northern Ghana', *BMC Pregnancy and Childbirth*, 13. Available at: <https://doi.org/10.1186/1471-2393-13-72>.
- Takehima, T. *et al.* (2021) 'Oxidative stress and male infertility', *Reproductive Medicine and Biology*. Available at: <https://doi.org/10.1002/rmb2.12353>.
- Thurmond, A.S. (2013) 'Fallopian tube catheterization', *Seminars in Interventional Radiology*, 30(4). Available at: <https://doi.org/10.1055/s-0033-1359732>.
- Turan, I.T. (2023) 'Intrauterine insemination', in *Holistic Approach to Assisted Reproductive Technology*. Available at: [https://doi.org/10.5005/jp/books/18020\\_50](https://doi.org/10.5005/jp/books/18020_50).
- Unuane, D. *et al.* (2011) 'Endocrine disorders & female infertility', *Best Practice and Research: Clinical Endocrinology and Metabolism*. Available at: <https://doi.org/10.1016/j.beem.2011.08.001>.
- Vitale, S.G. *et al.* (2016) 'Comment on "Disability, psychiatric symptoms, and quality of life in infertile women: a cross-sectional study in Turkey"', *Shanghai Archives of Psychiatry*, 28(6). Available at: <https://doi.org/10.11919/j.issn.1002-0829.216083>.
- Vitale, S.G. *et al.* (2023) 'Endometrial biopsy: Indications, techniques and recommendations. An evidence-based guideline for clinical practice', *Journal of Gynecology Obstetrics and Human Reproduction*. Available at: <https://doi.org/10.1016/j.jogoh.2023.102588>.
- Yang, A.M. *et al.* (2021) 'Letrozole for Female Infertility', *Frontiers in Endocrinology*. Available at: <https://doi.org/10.3389/fendo.2021.676133>.
- Yatsenko, S.A. and Rajkovic, A. (2019) 'Genetics of human female infertility', *Biology of Reproduction*. Available at: <https://doi.org/10.1093/biolre/ioz084>.
- Yilmaz, S. *et al.* (2018) 'Safety of clomiphene citrate: a literature review', *Cytotechnology*. Available at: <https://doi.org/10.1007/s10616-017-0169-1>.