Poonam Shodh Rachna(ISSN 2456-5563)
(A Multidisciplinary, Peer Reviewed and Refereed Research Journal)
Vol. 3, Issue.V, May 2024, PSR-2405051

FEMALE INFERTILITY AND ITS CAUSES

Suneetha Devi Kumpatla, Department Of Clinical Embryology
And Reproductive Genetics, Rayat- Bahra University
Dipneet Kaur (HOD), Department Of Clinical Embryology
And Reproductive Genetics, Rayat- Bahra University
Dr. Sunil Kumar, Department Of Clinical Embryology
And Reproductive Genetics ,Rayat-Bahra University

ABSTRACT:

Infertility is a complex issue that can be caused by the various factors. The inability to conceive after 12 months or 1 year of regular unprotected intercourse that is either primary and secondary infertility affects so many women's. This paper provides a comprehensive review of female infertility and its causes. The main aim of this review is to generate information which could act as guidline in the causes of female infertility.
KEY WORDS: *Infertility, causes of infertility, ART.*

INTRODUCTION:

The **World Health Organization (WHO**) defines infertility as a medical condition of the reproductive system caused by the inability to have a clinical pregnancy after 12 months or more of frequent, unprotected sexual activity. The inability to conceive leads to a number of significant and predictable consequences, including the fact that infertile couples experience anxiety and depression more frequently than fertile ones. Assisted reproductive technologies, or ARTs, are also readily available for the treatment of infertility but are expensive. A number of these issues included the fertility status of numerous individuals around the nation. Few research have addressed this health issue despite the subject's mental, social, and economic proportions .Infertility can result from a variety of medical conditions, injuries to the fallopian tube, fertilization, and ovulation. Interference, or hormonal turbulence, can also occur. Incapable of conceiving or having difficulty conceiving is a physically and psychologically uncomfortable condition to the women and men.

Normal fertility is contingent upon the male producing an adequate quantity of healthy, motile sperm, delivering those cells into the vagina, the sperm successfully traveling via the uterus and into the fallopian tubes, and one of the sperm entering a normal ovum (egg). For a pregnancy to be successful, the fertilized egg must next embed itself in the lining of the woman's uterus. A couple may become infertile due to issues at any one of these stages.

Ovulatory abnormalities are one of the main causes of infertility in women. The delicate balance needed for conception is upset by irregular or absent ovulation, which affects the regularity of the menstrual cycle and lowers the likelihood of successful fertilisation. The path of the egg and sperm is impeded by structural obstacles, such as clogged fallopian tubes, which prevents their merger. The condition known as endometriosis, in which tissue resembling the lining of the uterus grows outside the uterus, further complicates the picture of fertility. Hormonal dysregulation, frequently linked to disorders such as polycystic ovarian syndrome (PCOS), significantly impacts fertility. The complex balance of hormones necessary for ovulation and implantation might be disturbed, resulting to difficulty in conception. Age, too, appears as a significant element.

A thorough approach is required to diagnose female infertility, entailing a close review of medical history, physical examinations, and a variety of reproductive testing. Imaging investigations, hormonal assays, and other diagnostic instruments make up the diagnostic toolkit used to solve the mysteries of infertility. When a diagnosis is made, a variety of difficulties are frequently revealed, ranging from clearly defined medical disorders to cases of infertility.

The field of assisted reproductive technologies (ART) presents a hopeful picture of female infertility. An egg is fertilised with sperm outside the body by in vitro fertilisation (IVF) and other assisted reproductive technologies (ART), and the resulting embryo is then implanted into the uterus. These technologies offer opportunities, but there is no assurance that they will be successful, and there may be limitations on how easily they may be used.

CAUSES OF FEMALE INFERTILITY

ENDOMETRIOSIS:

The medical condition known as endometriosis occurs when endometrial tissue grows outside of the uterus, usually in another location in the pelvis. It can make getting pregnant difficult and result in excruciating pelvic pain. Endometrioma are lumps of endometrial tissue that develop outside of the uterus. The pouch of Douglas, a small region between the uterus and the rectum, is where endometrial tissue most frequently settles. We refer to this as chocolate cysts when endometrial tissue is found in the ovaries. The **American Society of Reproductive Medicine (ASRM)** states that endometriosis can occur in four different stages: minimal, mild, moderate, and severe. Endometriosis has been linked to issues including constipation, infertility, unpleasant sex, and pelvic pain.

The endometrial lining begins to break down during menstruation and typically exits through the cervix and into the vagina. However, in certain women, it may flow backward through the fallopian tubes and into the pelvis; this is known as **RETROGRADE MENSTRUATION**. Following its passage from the fallopian tube into the pelvis, endometrial tissue seeds itself, resulting in little pockets of endometrial tissue. Then it spreads via the lymphatic system in a manner akin to the metastasis of cancer, or it might be that cells in other places undergo a process known as CELL METAPLASIA, which converts those cells from normal cell types to endometrial cells. The cells that have colonized beyond the uterus are still hormone-responsive.

A cyclical pain that is similar to or slightly before menstruation is caused by cells that have settled outside the uterus and are responding to hormones in the same way as the endometrium inside the uterus. These cells begin to develop and thicken, and during menstruation, they also begin to shed. This bleeding elsewhere in the body causes irritation and inflammation. Additionally, adhesions from inflammation might cause a mechanical disturbance in fertility. Women with moderate endometriosis have follicular abnormalities, such as aberrant follicular development and decreased follicular size. Women who have endometriosis and are infertile also experience irregular cycles.

As we previously noted, pelvic pain and infertility are common presenting symptoms of endometrioma, and the best course of treatment for both is surgery. Additionally, there are a number of treatment options available, depending on the extent of the damage and its outcome. For ovarian damage, the two options are cyst wall ablation and cystectomy; infertile women with ovarian endometriomas are treated surgically with this medical therapy, which does not appear to improve fertility after treatment. Takahiro et al. conducted research on the effects of ovarian endometrioma on oocytes and the success of IVF pregnancies. They came to the conclusion that endometriosis influences oocyte quantity but not embryo quality or pregnancy result.

ECTOPIC PREGNANCY:

The term "ectopic pregnancy" refers to pregnancy in which the embryo implants and develops outside of the uterus. Although an ectopic pregnancy can develop anywhere, the fallopian tubes account for 95% of ectopic pregnancy cases. However, 70% of ectopic pregnancies occur in the ampulla, which is also the site of fertilization in tubal ectopic pregnancies. Furthermore, 12% at the isthamic region, 11% at the fimbrial region, and 2% at the interstitial zone. The most frequent non-tubal site of ectopic pregnancy is the ovaries, and the least common sites are the cervical or c-section scars.

Among the ectopic pregnancies are,

Cornual pregnancies, which occur in the fallopian tube's interstitial space, and

Angular pregnancies, which occur intrauterinely close to the angle of the uterus.

Heterotrophic pregnancy refers to a combination of intrauterine and ectopic pregnancy, where one pregnancy develops inside the uterus and the other outside. This condition is primarily caused by assisted reproductive techniques like in vitro fertilization; if multiple embryos are transferred, such as three or four, there is a risk of heterotrophic pregnancy.

Although the possibility of an ectopic pregnancy during IVF is higher with fresh embryo transfer and lower with frozen embryo transfer, the total rate of ectopic pregnancy during IVF is approximately 1.3%. The most frequent risk factors for ectopic pregnancy are endometriosis, prior tubal surgery, smoking, IV drug misuse, genital TB, many partners, and failure of contraceptives. These women are at risk of ectopic pregnancy because to these conditions, which causes improper implantation.

Generally, the tubal ectopic pregnancy ends earliest in isthamus 6 weeks, where as the longest survival in interstitial space is about 12 weeks, and also longest survival period at abdominal cavity till term means upto 9 months. The diagnosis of the ectopic pregnancy is based up on combination of measurement of human chorionic gonadotropic in serum and findings in the transvaginal ultrasonography. During treatment where the unruptured ectopic are treated with methotrexate which comes under medical management, this is a primary treatment and, in some cases, surgical management is also required.

UTERINE FACTOR INFERTILITY:

Uterus is very important for pregnancy because it helps for developing of fetus. But if uterus is not present or if it is not working properly, it's difficult to get pregnant for women this condtion is known as uterine factor infertility. There are two types of uterine factor infertility are there

Congenital uterine factor infertility
Acquired uterine factor infertility

Congenital Uterine Factor Infertility –

If the women is born without uterus this condition is known as **Mayer Rokitansky – Küster – Hauser –syndrome [MRKH]** or if the uterus is there also it will not function properly due to an issue that occurred during fetal development for example the shape of the uterus is not good it can contribute to infertility but in this condition, there is a chance to get pregnancy.

Acquired uterine factor infertility –

IF any changes that occurs during life due to hysterectomy, and some of the factors like scar tissue, radiation damage, uterine fibroids, polyps, infections, any other injuries which leads to prevent pregnancy. The women with these conditions do not get menstrual periods the symptoms are vary from person to person because it depends up on the cause.

CERVICAL FACTOR INFERTILITY:

In cervix when there is an infection, incorrect or insufficient cervical mucus can contribute to infertility, and about 3-5% of all women are suffering with the cervical factor infertility. The endocervical glands which secrete mucus, can be destroyed by a persistent infection. The leukocyte infiltration that follows can also kill sperms and reduce their motility. Immunoglobulin G (IgG) and IgA, antisperm antibodies, may be found in cervical mucus these make the spermetozoa move erratically and prevent them from penetrating the mucus. And also using of anti estrogens can leads to the decreasing of cervical mucus production, because the mucus production in the cervix is basically depends up on the hormone of estrogen, for example during ovulation induction clomiphene citrate medication will give to that patient this a type of anti-oestrogen.

For investigation of presence antisperm antibody postcoital test will do that is sims or huhner test. In this we will check the receptivity of the cervical mucus with the sperm, in this we should see atleast 15-20 highly progressive motile sperms, but if the antibody antisperms are present the sperms become completely immotile or they show shaking moment. For avoiding the

antisperm antibody problem its better to use the barrier methods. In ART for female cervical factor infertility IUI is the best method and which give a better positive result.

TUBAL FACTOR INFERTILITY

Tubal factor infertility refers to difficulties in conception caused by abnormalities or blockages in the fallopian tubes. The fallopian tubes play a crucial role in the reproductive process, facilitating the passage of eggs from the ovaries to the uterus. When these tubes are obstructed or damaged, the sperm may struggle to reach the egg, leading to infertility. Various factors can contribute to tubal issues, including pelvic inflammatory disease (PID), which often results from sexually transmitted infections (STIs) like chlamydia or gonorrhea. PID can cause scarring and adhesions in the fallopian tubes, hindering the normal movement of eggs and sperm.

Additionally, endometriosis, a condition where tissue similar to the uterine lining grows outside the uterus, can impact the fallopian tubes. The presence of endometrial tissue in or around the tubes may cause blockages or distort their anatomy, affecting fertility. Surgical procedures, such as tubal ligation (a method of permanent contraception) or surgeries to treat other reproductive issues, can also lead to tubal factor infertility. While tubal ligation is intended to be irreversible, there are cases where attempts at tubal reversal or in vitro fertilization (IVF) are explored for those seeking fertility restoration.

HORMONAL IMBALANCE:

An important factor in female infertility is hormonal imbalance. Polycystic Ovary Syndrome (PCOS), a prevalent reason where high testosterone levels interfere with normal ovulation, is one such cause. PCOS is frequently accompanied by insulin resistance, which further disrupts hormone balance. Menstrual cycle irregularities, which are frequently associated with hormonal imbalances, are another factor. The luteinizing hormone (LH) and follicle-stimulating hormone (FSH) produced by the pituitary gland can malfunction and prevent eggs from releasing normally.

Fertility can also be impacted by thyroid conditions. Anovulatory periods and fluctuating thyroid hormone levels are symptoms of hypothyroidism. Conversely, the menstrual cycle may be disturbed by hyperthyroidism, which is characterised by elevated thyroid hormones.
Adrenal disorders, such as congenital adrenal hyperplasia, can cause an overproduction of androgens, impacting the ovarian function and fertility. Additionally, hormonal contraceptives, when discontinued, may cause a temporary delay in the return of normal ovulation. The delicate balance between estrogen and progesterone is crucial for a healthy menstrual cycle and successful conception. Estrogen prepares the uterine lining for implantation, while progesterone supports the early stages of pregnancy. Any disruption in this balance can hinder fertility.

Hormonal imbalances can be caused by environmental variables that imitate or interact with natural hormones, such as exposure to endocrine-disrupting substances. These substances are present in common goods like plastics, insecticides, and some cosmetics. Taking care of the underlying problem is often necessary when treating hormone abnormalities. Hormone levels can be positively impacted by lifestyle changes such as stress management, regular exercise, and a balanced diet. In certain situations, doctors may prescribe drugs to cause ovulation, such as clomiphene citrate. If previous treatments are ineffective for a woman with significant hormonal abnormalities, she may consider in vitro fertilisation (IVF). In vitro fertilisation (IVF) is the process of inducing numerous eggs from the ovaries, which are then fertilised outside body and placed into the uterus. For the identification and management of hormonal imbalances, routine monitoring and consultation with a reproductive endocrinologist are essential.

ANOVULATION:

Ovum is needed for pregnancy, but anovulation means during menstrual cycle the egg does not release from ovary if egg is not there fertilization is not happen so there is no opportunity for pregnancy so it leads to the infertility. The World health organization categorizes 4 types which comes under anovulation.

1.Hypogonadotropic Hypogonadism Anovulation

2.Normogonadotropic Normoestrogenic Anovulation
3.Hyper Gonadotropic Hypoestrogenic Anovulation
4.Hyperprolactinemic Anovulation

1. Hypogonadotropic Hypogonadism Anovulation:

is generally a hypothalamic amenorrhea this condition is due to the low level of follicle stimulating hormone [FSH], and luteinizing hormone these secretions are depends up on the GnRh which stimulate the anterior pituitary gland. If these hormones releases in normal range then only ovulation will occur properly .if it is not it leads to anovulation.

. 2.Normogonadotropic Normoestrogenic Anovulation IS PCOS this is the most common type

POLYCYSTIC OVARIAN SYNDROME [PCOS/PCOD]: PCOS was first discovered by stein Leventhal so it is also known as stein Leventhal syndrome. This is a most common endocrine disorder and which affects the women mostly up to 5-7%. The factors which leads to the PCOS in women are genetic factors, life style, and environmental factors

There are some criteria s are there to diagnosis the PCOS, one of the most followed criteria is ROTTERDAM criteria, according to this criterion there are 3 factors are there

1.Oligo amenorrhoea or amenorrhoea

2.hyperandrogenism

3.enlarged ovaries

If a woman has two of these three characteristics, we can diagnose her with PCOS. In most cases, anovulation is the cause of PCOS. This is caused by the abnormal release of endocrine hormones, specifically LH and FSH, which act on theca cells and granulosa cells, helping to secrete progesterone from the corpus luteium after ovulation and estrogen before. However, in PCOS, LH levels rise, secreting a higher amount of androgen production, which is then converted into estrogen with the aid of the enzyme aromatase. FSH levels fall, preventing follicles from maturing and preventing ovulation, which can result in infertility.

Insulin is also plays an important role in PCOS, which stimulate the theca cells and also the adrenal cortex for the production of androgen which gives negative feedback to the hypothalamus and pituitary gland so it leads to hormonal imbalance complications so ovulation is not occurs properly this is known as insulin resistance .Treatment for PCOS are life style changes for example if the women is overweight its better to decrease the weight and with medications like clomiphene citrate , metformin and surgery is laparoscopic ovarian drilling .

3.Hyper Gonadotropic Hypoestrogenic Anovulation

Menstrual abnormalities and anovulation are the results of low oestrogen levels and increased gonadotropins (FSH and LH). This syndrome is known as hypergonadotropic hypoestrogenic anovulation. Numerous factors, such as ovarian dysfunction, polycystic ovary syndrome (PCOS), premature ovarian failure, or specific hereditary disorders, can contribute to this illness. In addition to treating the underlying reason, treatment may involve hormone therapy to control the menstrual cycle.

4.Hyperprolactinemic Anovulation

High blood levels of prolactin hormone cause hyperprolactinaemic anovulation, a disorder that results in irregular menstruation and anovulation (lack of ovulation). The primary function of the hormone prolactin is to stimulate the production of milk in the mammary glands, but it also inhibits the secretion of gonadotropin-releasing hormone (GnRH), which in turn suppresses the pituitary gland's release of luteinizing hormone (LH) and follicle-stimulating hormone (FSH). This process helps regulate the menstrual cycle.

Elevated prolactin levels can interfere with the regular pulsatile release of GnRH, which reduces the secretion of FSH and LH, which are necessary for the formation of follicles and ovulation. Women who have hyperprolactinaemic anovulation may thus have irregular or non-existent menstrual cycles and struggle to conceive.

Hypothyroidism: Increased secretion of thyrotropin-releasing hormone (TRH), which promotes the release of prolactin, can result from an underactive thyroid gland.

CHROMOSOMAL ABNORMALITIES:

About 10-15% of infertile couples are affected by chromosomal abnormalities, which are a major cause of female infertility. Turner syndrome, a frequent chromosomal abnormality linked to female infertility, is typified by the absence or structural abnormalities of one X chromosome. Ovarian dysfunction is common in women with Turner syndrome, which can result in early ovarian failure and infertility.

One additional important disorder is 47, XXX, or Triple X syndrome, which is characterised by one extra X chromosome in females. Although many people with Triple X syndrome are fertile, some may have trouble conceiving. However, anomalies that can affect fertility in a mosaic pattern include 47, XYY and 45, X/46, XY mosaicism.

Translocations and inversions are examples of structural chromosomal defects that can interfere with normal chromosomal pairing during meiosis, raising the possibility of miscarriages or the production of eggs with uneven genetic makeup. Chromosomes 13, 14, 15, 21, or 22 Robertsonian translocations are especially linked to reproductive problems. Premature ovarian insufficiency can also result from disorders like fragile X syndrome, which is brought on by a mutation in the FMR1 gene and affects ovarian function. In women who are impacted, the increase of the CGG repeat in the FMR1 gene presents difficulties for conception.

For a successful conception and embryonic development, general chromosomal integrity is essential in addition to these particular chromosomal anomalies. Diagnosing possible reasons of female infertility requires screening for chromosomal abnormalities using methods such as chromosomal microarray analysis or karyotyping.

INFECTIONS:

Female fertility can be greatly affected by infections since they can disrupt different reproductive organs and processes. Pelvic inflammatory disease (PID) can result in inflammation and scarring of the fallopian tubes, impeding the normal flow of eggs. It is frequently brought on by sexually transmitted infections (STIs) such gonorrhoea and chlamydia. Infertility or ectopic pregnancies may arise from this. The vaginal environment can be changed by infections such as bacterial vaginosis, which can affect the balance of good bacteria and perhaps interfere with the implantation process. Genital ulcers can be brought on by sexually transmitted viruses, such as the herpes simplex virus (HSV), which also raises the risk of infection and inflammation.

Moreover, pelvic infections from systemic infections that are not limited to the reproductive organs, including tuberculosis, can result in tubal obstructions and issues with conception. In addition to potentially influencing fertility indirectly, chronic diseases such as polycystic ovarian syndrome (PCOS) have been linked to an increased vulnerability to infections. An immunological reaction brought on by infections can occasionally result in disorders such pelvic adhesions or ovarian dysfunction.

It is important to remember that preventing long-term reproductive problems depends critically on prompt diagnosis and appropriate treatment of infections. Maintaining reproductive health requires routine tests, safe sexual habits, and fast medical intervention for infections. Taking preventive measures and consulting a medical professional are the first steps in reducing the effect of infections on female fertility.

AFFECTS OF MEDICATIONS:

Some drugs may influence the hormonal balance of the body or interfere with the processes involved in reproduction, which may have an effect on the fertility of females. By inhibiting ovulation, hormonal contraceptives, including birth control pills, control the menstrual cycle. Even though these drugs are good at preventing conception, stopping them could take some time for fertility to return to normal.

NSAIDs (Non-Steroidal Anti-Inflammatory Medicines) may affect fertility by interfering with ovulation. Menstrual cycle disruption and reproductive hormone effects are potential side effects of certain chronic disease drugs, such as some antidepressants and antipsychotics.

Chemotherapy medications, which are necessary for the treatment of cancer, might damage the ovaries and decrease egg production, resulting in either temporary or permanent infertility. In a similar vein, radiation therapy to the pelvic region has the potential to harm reproductive organs and lower fertility

LIFE STYLE EFFECTS:

Female fertility can be greatly impacted by a number of lifestyle factors. Keeping a healthy body weight is essential since both being overweight and underweight can throw off the hormonal balance and interfere with conception. While regular exercise is important, overdoing it can potentially lead to problems with fertility. Smoking has been associated with lower fertility, resulting in lower egg production and quality. Overindulgence in alcohol can interfere with menstrual cycles and hormone levels, which may make conception more difficult.

A balanced, nutrient-rich diet is important for supporting reproductive health. Fertility may be hampered by inadequate intake of vital nutrients like iron and folic acid. In today's fast-paced environment, stress is often present and might throw off the hormonal balance needed for conception. Reproductive hormones may be impacted by irregular sleep patterns, thus getting enough sleep is essential.

Fertility can be impacted by environmental variables, including exposure to poisons and pollution. Long-term exposure to some chemicals, such as those in plastics and pesticides, can be harmful to reproductive health. Infertility can result from sexually transmitted infections.

Given that fertility often decreases with age, especially after the age of 35, age is a crucial issue. The chance of conception may drop if childbearing is postponed. Infertility can be exacerbated by diseases like endometriosis and polycystic ovarian syndrome (PCOS), which emphasises the significance of early detection and treatment.

In summary, keeping up a healthy lifestyle is critical to female fertility. This include reaching and keeping a healthy weight, eating a balanced diet, controlling stress, and staying away from dangerous

UNEXPLAINED INFERTILITY

The cause of unexplained female infertility is still unknown after a thorough medical study of the problem. It is a confusing issue. Infertility affects 10–15% of couples attempting to conceive, and in over one-third of these instances, female factors are the cause of the problem. Unexplained infertility is the diagnosis made when conventional reproductive tests are unable to pinpoint a specific cause.

Couples may experience emotional difficulties as a result of this disease .Infertility with no apparent cause could be caused by a number of things. It's possible that there are subtle hormone imbalances, irregular menstrual cycles, or uterine anomalies that are difficult to find with standard testing. There may also be problems with the quality of the eggs, fertilisation, or embryo implantation. Age, stress, and lifestyle choices. etc….

CONCLUSION:

A complicated and multidimensional problem, female infertility can result from a number of physiological, psychological, and environmental reasons. Millions of women worldwide experience the inability to conceive following a year of frequent, unprotected sexual activity, which involves emotional, social, and health risks. Ovulatory problems, anatomical anomalies, hormonal imbalances, and the age-related loss in fertility are common causes. Lifestyle factors that are linked to the increased incidence of female infertility include stress, overindulgence in exercise, and inadequate diet.

Technological developments in diagnosis, such as hormone tests, imaging methods, and genetic testing, have expanded our knowledge of the reasons of infertility and made customised treatment plans possible. Many couples find hope in assisted reproductive technologies (ART) such in vitro fertilisation (IVF), however there are ethical, emotional, and financial concerns with these procedures.

The treatment of female infertility requires a comprehensive strategy include not just medical treatments but also dietary adjustments, psychological support, and instruction. Family planning and fertility awareness are essential to enabling women to make decisions about their reproductive health that are well-informed. Female infertility can be prevented and managed with the help of public health programmes that emphasise environmental toxicity reduction, healthcare access, and education.

The emotional toll that infertility causes is frequently exacerbated by social stigmas, which the value of encouraging candid communication and strong support systems. To properly address this global health concern, collaboration between academics, politicians, communities, and healthcare providers is vital.

In conclusion, a holistic approach that takes into account the physical, social, and psychological aspects of female infertility is necessary to comprehend and treat the condition. Through research advancement, education promotion, and the creation of a nurturing atmosphere, society can strive to eliminate obstacles.

REFERENCES :

1.https://www.ncbi.nlm.nih.gov/books/NBK556033/
2.https://www.who.int/news-room/fact-sheets/detail/infertility
3.https://bmcwomenshealth.biomedcentral.com/articles/10.1186/s12905-019-0805-3
4.https://www.yalemedicine.org/clinical-keywords/female-infertility
5.https://hal.science/hal-03788854v1/file/jcm-11-04907-v2.pd
6.https://www.researchgate.net/publication/210090747_Female_infertility_and_its_treatment_by_alternative_medicine_A_review
7.https://www.researchgate.net/publication/352172696_Uttarbasti_an_Advance_Therapy_for_Mnagement_of_Vandhayatva_Female_Infertility_A_clinical_Review
8.https://www.researchgate.net/publication/350996286_Recent_Updates_in_Female_Infertility_A_Short_Review_of_Literature
9https://link.springer.com/chapter/10.1007/978-1-59745-108-6_4
10.https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2907557/
11.https://my.clevelandclinic.org/health/diseases/14523-hirsutism
12.https://www.researchgate.net/publication/272309469_**The_Evaluation_and_Treatment_of_Cervical_Factor_Infertility_A_Medical-Moral_Analysis**
13.https://www.scielo.br/j/medical/a/qjRg5mV765Dvs5tYjCtBwyC/?lang=en&format=pdf
14.https://www.fertstert.org/article/S0015-0282(97)00269-0/pdf
15.https://www.semanticscholar.org/paper/The-Evaluation-and-Treatment-of-Cervical-Factor-Mirkes-Yeung/efc9dd221657fa54743dc8362c97f931af
16. Chandra A, Copen CE, Stephen EH. Infertility and impaired fecundity in the United States, 1982-2010: data from the National Survey of Family Growth. Natl Health Stat Report. 2013Aug14;(67):1-18,1p.following
17. Santoro N, Filicori M, Crowley WF. Hypogonadotropic disorders in men and women: diagnosis and therapy with pulsatile gonadotropin-releasing hormone. Endocr Rev. 1986 Feb;7(1):11-23
18.Perkins RB, Hall JE, Martin KA. Neuroendocrine abnormalities in hypothalamic amenorrhea: spectrum, stability, and response to neurotransmitter modulation. J Clin Endocrinol Metab . 1999 Jun; 84(6)

19.Hull MG. Epidemiology of infertility and polycystic ovarian disease: endocrinological anddemographicstudies. GynecolEndocrinol. 1987Sep;1(3):235-45.
20.Rotterdam ESHRE/ASRM-Sponsored PCOS consensus workshop group. Revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome(PCOS). HumReprod. 2004Jan;19(1):41-7
21.Bulun SE. Endometriosis. N Engl J Med. 2009 Jan 15;360(3):268-79.
22. Holoch KJ, Lessey BA. Endometriosis and infertility. Clin Obstet Gynecol. 2010 Jun;53(2):429
23.Practice Committee of the American Society for Reproductive Medicine. Definitions of infertility and recurrent pregnancy loss: a committee opinion. Fertil Steril. 2013 Jan; 99(1) :63.
24. Berga SL, Marcus MD, Loucks TL, Hlastala S, Ringham R, Krohn MA. Recovery of ovarian activity in women with functional hypothalamic amenorrhea who were treated with cognitivebehaviortherapy. FertilSteril. 2003Oct;80(4):976-81
25.Mol BW, Swart P, Bossuyt PM, van der Veen F. Is hysterosalpingography an important tool in predicting fertility outcome? Fertil Steril. 1997 Apr;67(4):663-9. Hull MG.
26.Epidemiology of infertility and polycystic ovarian disease: endocrinological and demographicstudies. GynecolEndocrinol. 1987Sep;1(3):235-
45.
27.Practice Committee of the American Society for Reproductive Medicine. Definitions of infertility and recurrent pregnancy loss: a committee opinion. Fertil Steril. 2013 Jan;99(1):63
28.Practice Committee of American Society for Reproductive Medicine in collaboration with Society for Reproductive Endocrinology and Infertility. Optimizing natural fertility. FertilSteril. 2008Nov;90(5Suppl):
29.Wathen NC, Perry L, Lilford RJ, Chard T. Interpretation of single progesterone measurement in diagnosis of anovulation and defective luteal phase: observations on analysis of the normal range. .
30.https://www.sciencedirect.com/topics/medicine-and-dentistry/female-infertility
31.https://www.pfcla.com/causes-of-female-infertility