

Review of Female Infertility: Risk Factors and Management

Suhail Iqbal¹, Heena Kaurani², Mehak Ayub Malik³, Divya Chauhan⁴

How to cite this article:

Suhail Iqbal, Heena Kaurani, Mehak Ayub Malik et al./Review of Female Infertility: Risk Factors and Management./ Indian J Obstet. Gynecol. 2021;9(2):39-43.

Authors Affiliation: ¹Senior Resident, ³Junior Resident, Department of Obstetrics and Gynecology, Government Medical college, Baramulla, Jammu & Kashmir 191202, India, ²Senior Resident, Department of Obstetrics and Gynecology, Dr Sampurnanand Medical college, Jodhpur, Rajasthan 342003, India, ⁴Senior Resident, Department of Obstetrics and Gynecology, University College of Medical Sciences and Guru Teg Bahadur Hospital, Delhi 110095, India.

Corresponding Author: Suhail Iqbal, Senior Resident, Department of Obstetrics and Gynecology, Government Medical college, Baramulla, Jammu & Kashmir 191202, India.

Email: isuhaillove@gmail.com

Abstract

Infertility is a major health problem in couples of reproductive age group. Female factor is responsible for most of the cases of infertility. This review is done to enlighten the various risk factors causing infertility and its management. The aim of this review is to give information about female infertility to make it easy to evaluate a case of infertility. The conclusion is made from the review that by living healthy lifestyle, reducing body weight and proper treatment of medical diseases and sexually transmitted diseases, fertility can be achieved in infertile woman.

Keywords: Fertility; Female infertility; Laparoscopy; Hysteroscopy.

Introduction

"Without my kids, my house would be clean, my wallet would be full, but my heart would be empty." Child bearing and raising of children are associated with feeling of happiness and completeness. Reproduction is a very important part of human's life. After getting married, almost every couple expect their own babies. But it is impossible to predict when an individual couple will succeed in achieving pregnancy. In our society, the pressure to conceive is directed towards the woman, if she is unable to bear a child, she has to suffer a lot. In many societies, childless couples have to face social isolation which is a cause of feeling of guilt and distress to these couples. Infertility is a medical problem that involves both the couples

and both remain involved even if only one person needs medical treatment. It is like a chronic illness that uses up a large amount of couple's resources; emotional and financial. It takes a considerable amount of time, money, physical and emotional energy.

Human fertility compared with other species of animal kingdom is, unfortunately low.¹⁻⁴ Today infertility is a common problem that touches deeply the soul of couples involved in this. In recent years, the number of couples seeking treatment for infertility dramatically increased due to factors such as postponement of childbearing in women, development of newer and more successful techniques for infertility treatment and increasing awareness of available services.

Infertility is defined as inability of a couple to conceive after 12 months of regular intercourse without use of contraception in women less than 35 years of age; and after 6 months of regular intercourse without use of contraception in women 35 years and older.⁵ Infertility affects around 8-12% of the couples of reproductive age group.⁶ According to WHO, the prevalence of infertility ranges from 3.9 to 16.8% in India.⁷

It is observed that 80% of normal couples achieve conception within a year. 50% conceive within 3 months of regular, unprotected intercourse, 75% in 6 months and 80-85% conceive within a year. Infertility is classified as primary if conception has never occurred and secondary if the patient

fails to conceive after having achieved a previous conception.

The optimal age for conception in a woman is 20 to 35 years. The fertility rate reduces after the age of 40 years. So, it is necessary to investigate after 6 months of apparent infertility in a woman near or over the age of 35 years, instead of waiting for a year.

Events required for the occurrence of pregnancy

- Egg must develop in woman's ovary.
- The egg should be released into the fallopian tube each month (Ovulation).
- The egg must be fertilized by man's sperm into the fallopian tube.
- The fertilized egg must be able to travel through the fallopian tube.
- Implantation of the fertilized egg in the lining of the uterus.
- If there is interruption in any of these events, it will result in infertility.

Factors causing Infertility in women

A woman's ability to get pregnant can be affected by many factors which are as follows:

Age: Fertility decreases with increasing age. Female fertility is at its peak between ages of 18 and 24 years.⁸ The decline in fertility begins in the early 30 and accelerates during the late 30s and early 40s. It occurs due to decrease in quantity and quality of eggs. Increasing age is also associated with chromosomal errors which leads to spontaneous pregnancy loss.

Weight: Adequate nutrition is necessary in early life for fertility. Excessive weight loss or excessive weight gain both conditions can cause ovulatory dysfunction. Estrogen is produced by primary sex organs and fat cells.⁹ Thus obesity or high body fat causes increase in estrogen production which the body interprets as birth control. So, the chances of getting pregnant decreases. Too little body fat is associated with insufficient estrogen production, so menstrual irregularities and anovulatory cycle occurs which leads to infertility.

Addiction: Smoker women do not conceive as efficiently as nonsmoker women. Infertility rate is about two-fold higher in female smokers as compared to nonsmokers. Folliculogenesis is affected by cigarette smoking. Smoking also affects transport of embryo, receptivity of endometrium and uterine blood flow. Alcohol intake cause

elevation in estrogen level.¹⁰ Increase in estrogen results in decrease in FSH secretion which suppress folliculogenesis and cause anovulation.¹¹ Use of cocaine and marijuana also has effect on fertility.

Environment: Occupational exposure to toxic chemicals like pesticides, silicones, chlorinated hydrocarbons and volatile organic solvents can cause infertility.

Dyspareunia: Dyspareunia means difficult and painful coitus. It is itself a cause for infertility because this condition reduces the number of sexual activities. It can be due to painful lesion of vulva, vagina, cervix, adnexa and uterus. Functional spasm of sphincter vagina (vaginismus) also causes dyspareunia.

Congenital structural defects in genital tract: Absent or septate vagina, hypoplasia or absent uterus are obvious causes of infertility. These structural defects occur due to Mullerian agenesis.

Sexually transmitted diseases (STD): Sexually transmitted diseases are also important cause of infertility. These diseases are transmitted through sexual contact with the infected partner. The offending agent can be bacteria, virus or parasite. Some important STDs are Herpes, Syphilis, Chlamydia, Gonorrhea, Condylomata acuminata, Trichomoniasis, HIV). Ascending infection of Gonorrhea and Chlamydia is responsible for tubal damage thus leading to infertility.

Pelvic inflammatory disease (PID): Pelvic inflammatory disease implies inflammation of the upper genital tract involving the uterus and adnexa. The most common cause of PID is sexually transmitted diseases. Gonococcal and chlamydia infections are the most common. These infections result in tubal blockage, tubal damage, adhesions, abscess formation and eventually leading to infertility.

Hyperprolactinemia: Increase in level of prolactin causes oligomenorrhea or amenorrhea. Hyperprolactinemia can be due to macroadenoma of pituitary gland or other intracranial pathology.

Hypothyroidism: Hypothyroidism is prevalent in 2% to 4% women of reproductive age group. It leads to menstrual irregularities and anovulation. Subclinical hypothyroidism and the presence of antithyroid antibodies are associated with increased rates of infertility and spontaneous pregnancy loss.

Hypogonadotropic hypogonadism: Dysfunction within the hypothalamic pituitary axis causes decrease level of serum FSH, LH and estradiol which leads to anovulation. This condition is

known as hypogonadotropic hypogonadism. Which occurs due to physiological and pathological conditions. Stress, extreme weight loss, anorexia, excessive exercise, and low BMI are all associated with functional hypothalamic suppression, so good nutrition and optimal body weight should be encouraged to restore ovulation.^{12,13} Other causes are pituitary adenoma, craniopharyngioma, other central space occupying lesions, AV malformations and congenital hypothalamic failure (Kalman syndrome).

Ovarian factors: Ovarian factors are responsible in 30% to 40% cases of female infertility. Menstrual irregularities are suggestive of anovulation or oligo ovulation. Menstrual dysfunction is present in 18% to 20% of the general population.¹⁴ PCOD, corpus luteal phase defects and luteinized unruptured follicular syndrome are some important ovulatory factors causing infertility.

PCOD: Polycystic ovarian disease is the most common cause of oligo ovulation and anovulation in infertile women. Features of PCOD are polycystic ovaries, hyperandrogenism, hyperandrogenemia, elevated serum LH:FSH ratio and hyperinsulinemia.

Corpus luteal phase defect: It occurs in 3% to 4% of infertile women. It occurs either due to deficient progesterone or shorter duration of luteal phase. This defect is seen in pituitary hormone deficiency, hyperprolactinemia, excess luteolysis, hypothyroidism, clomiphene therapy and IVF programme.

Luteinized unruptured follicular syndrome: In this ovum does not release from follicle (trapped ovum) but regular menses and presumptive evidence of ovulation occurs in an infertile woman.

Premature ovarian failure: It is also called primary ovarian insufficiency. It occurs when the ovaries stop functioning normally before the age of 40. In this condition ovaries do not produce normal amounts of the hormone estrogen or release eggs regularly and leads to infertility.

Tubal factors: Tubal factors are present in 25% to 35% cases of infertility. Noninfectious causes for tubal factors include tubal endometriosis, salpingitis isthmica nodosa, tubal polyps, tubal spasm and intratubal mucin debris.¹⁵ Gonorrhoeal and chlamydial infections or salpingitis following septic abortion and puerperal infections are common causes of fallopian tube blockage. Genital tuberculosis also causes tubal blockage. Peritubal adhesions and fimbrial end blockage can cause infertility.

Uterine factors: Uterine factors are responsible for almost 15% cases of infertility. These include endometrial hyperplasia, endometrial polyp, fibroids, intrauterine synechiae (Asherman syndrome) and congenital uterine anomalies. The uterine fibroid which causes infertility is a cornual fibroid blocking the medial end of the fallopian tube, submucous fibroid and cervical fibroid distorting the passage of the sperms. Asherman syndrome can occur due to infections, vigorous curettage, postabortal and puerperal infections and also due to packing of the uterine cavity to control PPH. Endometrial tuberculosis is another cause of infertility.

Cervical mucus: If cervical mucus contains antibodies against sperm, it causes infertility.

Cervical factors: These are responsible for about 5% cases of infertility. The normal position of cervix and its patency are required for fertility. Cervical infections (cervicitis) from STDs are also involved in infertility.

Endometriosis: It is the condition in which ectopic endometrial tissue develops outside the cavity of the uterus. It impacts on fertility by affecting tubal function and motility, inhibiting ovulation and ovum pick up by fimbria. Deep seated endometriosis causes dyspareunia which reduces frequency of sexual intercourse. In advanced stage of endometriosis, macrophages present in peritoneal fluid engulf the sperms or immobilize them.

Radiotherapy and chemotherapy: Radiotherapy and drugs used in chemotherapy causes decrease in ovarian reserve and causes infertility.

Drugs: Long term use of nonsteroidal anti-inflammatory drugs (NSAID) like Ibuprofen, aspirin and antipsychotic drugs causes infertility.

Diagnosis

In every case of infertility, both male and female partner should be included during workup. Before advising any invasive test to female partner, male factor of infertility should be excluded first.

History: Patient should be inquired about age, duration of marriage, menstrual history, coital difficulty previous obstetric history, history of postabortal or puerperal sepsis, medical history of tuberculosis, diabetes, thyroid disorder and STDs, history of abdominal or pelvic surgery and contraceptive practice.

Examination

General examination: Height and weight of the women should be measured. Acne, hirsutism, acanthosis nigricans, under development of secondary sexual characters, presence of secretion from breasts suggests hormonal disorder.

Systemic examination: It is done to rule out hypertension, chronic renal disease, thyroid dysfunction or other endocrinopathies.

Gynecological examination: The following features should be looked for; adequacy of hymenal opening, evidence of vaginal infections, elongation of cervix, cervical infection or tear, size of uterus, its position and mobility, presence of adnexal masses and presence of nodules in pouch of Douglas. Pap's smear should be taken and collection of vaginal and cervical discharge for culture should be done.

Tests to detect ovulation

- History of regular menstrual cycle

Basal body temperature: In ovulatory cycle, there is rise of temperature in postovulatory phase due to thermogenic effect of progesterone.

Cervical mucus study: Ovulatory cervical mucus is thin, elastic, and profuse.

Fern test: Sodium chloride levels in cervical mucus secreted under influence of estrogen are high around ovulation. These causes crystallization when it dries up on a glass slide.

Hormonal study: Plasma progesterone level above 3ng/ml on day 21-23 of an ideal 28 days cycle or 1 week prior expected onset of next menses confirms ovulation. There is also increase in LH level 2-3 times in pre ovulatory phase.

Endometrial biopsy: It can demonstrate secretory endometrial development which results from the action of progesterone and this implies ovulation.

Ultrasound: Irregular and decrease in size of monitored ovarian follicle and appearance of fluid in cul- de- sac characterizes ovulation.

Assessment of ovarian reserve: Parameters are: Age, Day 2 FSH, Antral follicle count, Inhibin B, Clomiphene citrate challenge test, Gonadotropin releasing hormone agonist stimulation test (GAST), Exogenous FSH ovarian reserve test (EFFORT), Ovarian biopsy.

Diagnostic tests for tubal infertility: Hysterosalpingography (HSG), saline infusion sonography (SIS), laparoscopy and chromotubation, combined laparoscopy and hysteroscopy, transcervical fallopscopy, selective

salpingography, colour doppler with SIS, virtual HSG.¹⁶

Methods to assess intrauterine pathology: Ultrasound, HSG, SIS, Hysteroscopy.

Diagnostic hysterolaparoscopy: In many cases, only physical examination and routine investigations are not sufficient to rule out the exact cause of infertility. Combined use of hysteroscopy and laparoscopy play an important role in diagnosis as well as treatment of unexplained infertility. Hysterolaparoscopy is useful in the direct visualization of uterine cavity and pelvis. Laparoscopy is the gold standard technique for detecting tubal and peritoneal pathologies.¹⁷ Laparoscopic surgery helps in the restoration of the normal tubo-ovarian anatomy by adhesiolysis. This alleviates the chronic pelvic pain and improves fertility.¹⁸ Endometriosis, peritubal adhesions and hydrosalpinx can be diagnosed and treated simultaneously by laparoscopy. On the other hand, hysteroscopy is useful for diagnosing intrauterine pathologies like congenital anomalies of uterus and small endometrial polyps which can be missed during other investigations. These can be treated at the same time of diagnosis. Cornual cannulation during hysteroscopy removes the proximal obstruction of the fallopian tube. In this way, both these techniques are complementary to each other and are diagnostic and therapeutic at the same time.

Treatment

- Patient should maintain a healthy lifestyle. She should take balanced and nutritious diet. Any kind of addiction should be avoided.
- Chronic medical illness like thyroid disorder, chronic renal disease, hypertension, hyperprolactinemia, diabetes mellitus etc. should be treated.
- Sexual transmitted disease should be treated.
- Mental health is also important. Patient should remain happy and stress free.
- Weight control is very useful in controlling infertility.
- Ovulation induction by using clomiphene citrate (CC), combination of CC and hMG, GnRH.
- Micronized progesterone for treatment of corpus luteal phase defect and luteinized unruptured follicular syndrome.
- Bromocriptine or cabergoline for treatment of hyperprolactinemia.

- Laparoscopic ovarian drilling in PCOD.
- Treatment of endometriosis medically or surgically.
- Laparoscopic tubal adhesiolysis, fimbrioplasty, Balloon tuboplasty and cannulation, tubal surgery for tubal blockage.
- Medical or surgical (myomectomy) treatment for fibroid.
- Artificial insemination by using husband's or donor sperms.
- Assisted Reproductive Techniques (ART): This is indicated in unexplained infertility, blocked tubes or abnormal tubes, male subfertility or in failure of ovulation. Techniques involved are IVF (In vitro fertilization), GIFT (Gamete intrafallopian transfer), ZIFT (Zygote intrafallopian transfer), ICSI (Intracytoplasmic sperm insemination).

Acknowledgement: Author acknowledges the role of study participants and timely completion of this study.

Authors Contribution: Iqbal S.(A), Kaurani H.(B), Malik M.(C)

"A" designed the research, collected and analysed data and co-wrote the paper, "B" analysed the data, co-wrote the paper, "C" designed the research, supervised the research and edited the final version of the paper, "D" supervised the research, provided valuable inputs, interpreted the data and edited the initial version of the paper

Source of Funding: None Declared

Conflict of Interest: None Declared

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