



An Overview of Risk Factors, Investigation and Management of Infertility in Women

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Abstract

This paper provides a review on infertility causes, investigations and treatment modalities. World health organization estimates, worldwide 60–80 million couples suffer from infertility. Infertility is not always a woman's problem. Both genders are equally responsible for the infertility cause. The male factor is the cause in approximately 23% Indian couples seeking treatment. No detectable cause can be traced after routine tests, which leaves the case as unexplained infertility. Causes of infertility are due to anatomical, physiological and genetic factors. The most common causes of impairment in fertility are uterine factors, menstrual and ovulation dysfunction. The etiology of infertility is an important criterion for recognition and characterization of infertile women. Advanced age, high body mass index, age of onset of sexual activity, prior pelvic surgeries and stress were the most significant risk factors associated with women's infertility. Female infertility factors are ovarian factors, Fallopian tube obstruction, Anomalies, Advanced ages (over 35 years), Life style and Exercise. The optimal management of infertility is an early and accurate evaluation of the reproductive tract, including uterine cavity, tubal patency and tubo-ovarian structures. Unexplained infertility couples have a chance of spontaneous conception. The pregnancy rate per cycle is estimated to be 0.9-4.1% with expectant management. It is observed that all couples with unexplained infertility will conceive with duration less than 2 to 3 years. Other treatment methods include ovulation induction with cc, gonadotrophins, Intra-uterine insemination and In-vitro fertilization.

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Introduction

Infertility is defined as the inability to conceive naturally after one year of regular unprotected intercourse. (1). WHO estimates, worldwide 60–80 million couples suffer from infertility (2).

Infertility is not always a woman's problem. Contribution towards infertility by the female factors, male factors and either a mixture of male and female factors or unknown factors is about one third each (3). Both genders are equally responsible for the infertility cause. Three major causes include

peritoneal disease seen in most of the infertile couples (4).

The chance to pregnancy depends on the length of sexual exposure, couple's age and frequency of coitus. The young aged couples have a 25% chance to conceive after 1 month of unprotected intercourse; 70% of the couple's conceive by 6 months, and 90% of the couples have a probability to conceive by 1 year. Only few couples of 5% will conceive after one and a half year or two years [4, 5].

male factor, ovulatory dysfunction and tubal-

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Infertility In India

WHO estimate of overall prevalence of primary infertility ranges between 3.9% and 16.8% (2). It was reported that 40% of infertility cases were related to men, 40% of women and 20% of both sexes (6). The male factor is the cause in approximately 23% Indian couples seeking treatment (7). In addition, over 25% of infertility cases, no detectable cause can be traced after routine tests, which leaves the case as unexplained infertility (8).

Female Infertility

Causes of infertility are due to anatomical, physiological and genetic factors. The most common causes of impairment in fertility are uterine factors, menstrual and ovulation dysfunction (10).

Female infertility can happen due to any of the following.

1. Fertilized egg or embryo fails to survive on the lining of the uterus.
2. Fertilized egg's inability to attach to the lining of the uterus.
3. Fertilized egg could not make its way to the uterus from ovary.
4. Egg production problems with ovaries (9).

Female Cycle

The normal female cycles are about 28 days long. Every 28 days, a bleed will occur and lasts for about 5 days. There are four hormones which control this cycle and they are controlled mainly by the hypothalamus. It acts on the pituitary gland to release Follicle stimulating hormone and Luteinizing hormone, the sex hormone that produce ovulation by stimulating the ovary (11).

Types Of Female Infertility

In women, two main types of infertility are seen. They are (1)

Primary Infertility:

It is a condition in which a couple has never been able to conceive.

Secondary Infertility:

It is a condition of cases where a couple has been successful in conceiving at least once, but unsuccessful after that.

Unexplained Infertility.

Unexplained Infertility

The cause of infertility is said to be unexplained when the following criteria are met:

Normal ovulatory function is established by means of basal body temperature measurement, changes in cervical mucus, serum luteinizing hormone (LH), mid-luteal progesterone levels, or during ultrasound there is an evidence of follicular rupture.

Semen analysis is normal

Establishment of Tubal patency by hysterosalpingography or laparoscopy (12).

Factors associated with female infertility:

The etiology of infertility is an important criterion for recognition and characterization of infertile women (13, 14). Advanced age, high body mass index, age of onset of sexual activity, prior pelvic surgeries and stress were the most significant risk factors associated with women's infertility (15).

Female infertility factors are:

Ovarian factors:

Polycystic Ovary Syndrome (PCOS)

Premature Ovarian Failure (POF):

Emotional stress

Body weight

High levels of the hormone Prolactin

Fallopian tube obstruction

Endometriosis

Tubal and peritoneal factors

Inflammatory diseases

Anomalies

Uterine anomalies

Tubule anomalies

Ovarian anomalies

Cervical anomalies

Advanced ages (over 35 years)

Life style

Exercise

Ovarian factors

Polycystic Ovary Syndrome (PCOS):

Polycystic ovary syndrome (PCOS) is a complex condition characterized by elevated androgen levels, irregular menstrual cycle, and/or small cysts on one or both ovaries (16).



Polycystic ovary syndrome causes infertility in young women and provides 70% of unovulation infertility (19), and 15.6% of primary infertilities (17,18).

Premature Ovarian Failure (POF)

The primary ovarian defect characterized by absent menarche or premature depletion of ovarian follicles and the loss of ovaries function before age of 40 is defined as premature ovarian failure (19,20).

High levels of the hormone Prolactin

Prolactin is a pituitary derived hormone and hyperprolactinemia, an endocrine disorder leads to infertility in women (21).

Body weight

Obesity is strongly associated with female infertility (22). Although, the mechanism underlying this relationship is largely unknown, but it is clear that fat cells produce estrogen (23). Both over and underweight women have irregular cycles in which ovulation is inadequate or it does not occur. Proper nutrition in early life is also a major factor for later fertility (24).

Emotional stress

The biological interaction between stress and infertility is due to the action of stress hormones on the hypothalamus-pituitary as well as on female reproductive organs. Stress hormones such as Catecholamines and the hypothalamic-pituitary-adrenal axis interact with hormones that are responsible for normal ovulatory cycles including gonadotropin releasing hormone, Prolactin, LH and FSH. Endogenous opiates and melatonin secretion are altered by stress and interfere with ovulation in normal ovulatory cycles. (25).

Tubal and peritoneal factors

Inflammatory diseases
Pelvic inflammatory diseases occur in 3.1% and 16.7% of primary and secondary infertility cases respectively (24). Genital infections represent one of the most important causes of infertility, affecting fallopian tubes, endometrial mucosa and sperm parameters (26, 27).

Endometriosis

Endometriosis can lead to anatomical distortions and adhesions. It has been suggested that endometriotic lesions release certain agents which are harmful for gametes or embryos (28). The most common causes responsible for infertility were tubal occlusion, endometriosis, per tubal and per ovarian adhesions (29).

Fallopian tube obstruction

The fallopian tube obstruction has been reported as a major cause of female infertilities. These women are unable to let the ovum and the sperm converge, thus making fertilization impossible (30).

Anomalies

Uterine anomalies

The uterine malformation is known as feminine genital abnormality caused by associate abnormal duct development throughout embryogenesis (31).

Tubule anomalies

The tubal blockage has been reported in 21.9% and 33.3% of primary and secondary infertility cases respectively (32).

Ovarian anomalies

Irregular menstrual cycles, acanthosis nigricans, hirsutism, polycystic ovary syndrome, a LH: FSH ratio of >1, and increased TSH or testosterone levels were the clinical findings associated with ovulatory dysfunction (33).

Cervical anomalies

Cervical stenosis might affect natural fertility by clogging the passage of semen into the uterus. Cervical stenosis complicates the intrauterine insemination (IUI) or in vitro fertilization (IVF) procedures in female infertility patients (34).

Advanced ages (over 35 years)

Age is an effective factor of woman's fertility. The woman's fertility peaks in the mid twenties, after which it starts to decline. As majority of women in particular, choose to delay childbearing, they will be faced to age-related fertility problems (35).

Life style

Exercise

Regular exercise is beneficial regardless of age, sex or body weight. However, there are evidences



confirming that excessive exercise may lead to adverse effects on the reproductive system and fertility (36).

First Line Investigation Of Female Infertility

The optimal management of infertility is an early and accurate evaluation of the reproductive tract, including uterine cavity, tubal patency and tubo-ovarian structures. Transvaginal hydrosalpingography is increasingly used to evaluate the uterine cavity. (37,38)

Ovarian function

Ovulatory dysfunction is one of the causes of infertility in 20% of couples. History of irregular menses or secondary amenorrhea is often present in women. When the menstrual cycle is either short or prolonged, is suggestive of disordered ovulation. There are numerous methods available to determine whether a patient is ovulating regularly. It is said that 'normal' ovulation is the development of a subsequent pregnancy. There are both direct and indirect methods of investigation. The detection of follicle rupture, either via laparoscopy or ultrasound is required to determine ovulation directly. There are number of methods to assess ovulation indirectly (39).

Basal body temperature (BBT)

Elevated progesterone levels during the 11 to 16 of the menstrual cycle cause the temperature of the body to rise 0.5-1.0 Deg F. This is the simplest test for ovulatory evaluation.

Urinary luteinizing hormone (LH)

The urinary LH surge occurs usually about one to two days prior to the rise in BBT and 12 to 60 hours before ovulation. The most sensitive use of the test requires emptying women bladder in the morning between 10am and 12pm. Fluid restriction is required to perform the test (40).

Luteal phase endometrial biopsy:

Luteal phase endometrial biopsy can be performed four days before expected menstruation. The histological appearance of secretory endometrial implies progesterone production following ovulation (41). The recognized diagnostic criteria of luteal phase defect is delay in maturation of longer than two days (42).

Serum follicle stimulating hormone (\pm LH)

Serum FSH test should be performed on any patient once fertility treatment is also contemplated. To measure 'ovarian reserve' day 3 FSH levels is widely accepted. FSH level of greater than 10 mIU/mL is evidence of impaired ovarian reserve (43).

Serum thyroid stimulating hormone (TSH)

Thyroid dysfunction is common in women of procreative age.. Hyperthyroidism or hypothyroidism may interfere with reproductive function significantly (44).

Serum prolactin

Amenorrhea and anovulation are caused by Hyperprolactinemia . The generally accepted normal range of serum prolactin is 30 to 40 ng/mL (600 to 800 mIU/mL) and it should be measured under basal conditions (45).

Tubal function

Tubal disease occurs in patients presenting with infertility of 15 to 20% (46).

Hysterosalpingogram (HSG)

HSG is the most widely used method to assess tubal patency. It is an outpatient x-ray procedure involving instillation of either water- or oil-based contrast media into the uterine cavity (47). It provides information about tubal patency and also delineates the uterine cavity.

Laparoscopy with chromopertubation

The 'gold standard' method of tubal assessment is the procedure, where a solution of methylene blue (or indigo carmine) is injected into the uterine cavity under laparoscopic vision and, hence, the fallopian tubes. Laparoscopy with chromopertubation determines peritubal adhesions or endometriosis that cannot be detected with a more conventional HSG (48).

Hysterocontrastsonography (HyCoSy)

To assess tubal patency high resolution transvaginal ultrasound in combination with echo-sensitive contrast agents is used. It provides information regarding the uterine cavity and tubal patency (49). HyCoSy when combined with a pelvic ultrasound assessment gives additional benefit (50). It is rarely possible to demonstrate the



complete length of the fallopian tube in one scanning plane (51).

Uterine assessment

Specific problems of the uterus are not common causes of female sub fertility. However, an assessment should be performed, especially before starting treatment. During the course of an HSG, the uterine cavity is usually defined and most developmental abnormalities can be identified. Disorders like polyps, sub mucous fibroids and intrauterine adhesions may also be seen. There are two predominant methods of assessing the uterus (52).

Transvaginal ultrasound

Transvaginal ultrasound is the investigation choice for assessing uterine and associated pelvic anatomy. It appears to be as effective as superior to laparoscopy for identifying uterine lesions. Three-dimensional ultrasound can be as effective as traditional diagnostic methods with respect to congenital abnormalities of the genital tract. Ultrasound have the advantage to assess uterus, endometrial and the ovaries (53).

Hysteroscopy

Hysteroscopy is the method of assessing the uterine cavity.

Different treatment options:

Expectant management:

Unexplained infertility couples have a chance of spontaneous conception. The pregnancy rate per cycle is estimated to be 0.9-4.1% with expectant management. (54, 55)

It is observed that all couples with unexplained infertility will conceive with duration less than 2 to 3 years (56).

Ovulation induction with clomiphene citrate

Clomiphene citrate is usually used for ovulation induction and has been shown to increase pregnancy rate from 1-2% to 5% per cycle in women with unexplained infertility (57).

Ovulation induction with gonadotrophins

Gonadotrophins used for ovulation induction are recommended to start with low dose of 50-70 IU and the dose is adjusted according to ovarian

response. (58). Follicular count and size are used for monitoring ovarian response. (59).

Intra-uterine insemination

Intra-uterine insemination is an alternative first choice of treatment of women with unexplained infertility (60). After standard Percoll gradient preparation of the semen, a catheter is passed via cervical canal and the washed sperm suspension at volumes of 0.5-2 ml is force-out into the uterine cavity (61). This can be combined with CC, gonadotrophins or both (62).

In-vitro fertilization

For couples with unexplained Infertility, In-vitro fertilization is recommended when other treatments have failed (63). IVF is useful for detect abnormalities in gametes and to evaluate the fertilizing capacity of spermatozoa and oocytes. Intracytoplasmic sperm injection (ICSI) is the treatment of Choice when no fertilization has occurred in a previous IVF attempt, and also in cases of low fertilization percentage with conventional IVF. The oviduct provide an optimized environment for fertilization and first cell divisions, and the embryo enter the uterine cavity at a more physiological time in the luteal phase than in IVF (64, 65).

Conclusion

Infertility is defined as the inability to conceive naturally after one year of regular unprotected intercourse. Infertility can have negative effects on couple's lives and it is important to improve their reproductive health. This study states it is necessary to evaluate and provide the accurate treatment.

Conflict of interest

None Declared

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