Recent Updates in Female Infertility: A Short Review of Literature

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Abstract

Infertility is defined as the inability to conceive after 1 year of unprotected intercourse. It has been estimated that 93% of healthy couples practicing unprotected intercourse should except to conceive within 1 year. Females presenting after this time should therefore be regarded as possibly infertile and should be evaluated. Although infertility is considered by some as primarily a woman's problem, men often contribute to and are also affected. Infertility problem often arise as a result of hormonal dysfunction of the hypothalamic-pituitary-gonadal axis. Human infertility is a complex problem, which has numerous consequences depending on the society and cultural background, age, hormone problems, environmental problem, gender, lifestyle, sexual history, of the people it affects. Infertility is a global public health concern this is partly due to its complexity in etiology as well as difficulty in preventing, diagnosing and treating it.

Keyword: *Female infertility, Testosterone, Endometriosis, Prolactin, PCOD*

Introduction

Parenthood is considered one of the most important life achievements in the Indian society.[1] It is widely accepted that human existence reaches completeness through a child and fulfils the individual's need for reproduction.[2] Infertility disrupts the basic social structure (Family-building) and there by the domestic and social economic wellbeing of a couple is not achieved. Although good documentation of the prevalence of infertility is lacking, it is generally believed that more than 70 million couples suffer from infertility worldwide. [2,3] In India the prevalence of primary infertility was 12.6 percent.[4] Conception normally is achieved within (12) months in (80-85) of couples who use no contraceptive measures.

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Females presenting after this time should therefore be regarded as possibly infertile and should be evaluated. Data available over the past (20) years reveal that in approximately (30%) of cases, pathology found in the women alone, and in another (20%) both the man and woman are abnormal. [5-6] The women reproductive years begin when she starts her menstrual cycle during puberty (about the age 13) years, and the ability to have a child usually ends around the age (45) years, although it is potentially possible for a women to be pregnant until her periods end with menopause (about the age 51) years. [7] Born girl already carries in her body about (400000) immature eggs (oocytes). These are stored in her ovaries in tiny fluid-filled sacs called follicles. Once she enters her reproductive years, she starts having monthly one egg (or, less commonly, more than one), which may join with a male motile sperm cell during fertilization and being a pregnant. [8] The development and release of the egg depend largely on a delicate balance of hormones (chemicals that signal the body organs to do a particular task). Some of these hormones are produced in the ovaries, others from the two glands in the brain, the

hypothalamus and the pituitary. [9] Primary infertility is a term used to describe a couple that has never been able to conceive after a minimum of one year of attempting to do so through unprotected intercourse. Causes of primary infertility include a wide range of physical as well as emotional factors. [10]

The principal causes are:

1. Ovulatory or hormonal abnormality: Failure of ovulation is the single most common cause of infertility in females. The normal ovarian cycle is so complex that even small deviations may disrupt the cycle and prevent ovulation. [11] Ovulatory disorders are most often caused by abnormality in one of the controlling hormone. However problems can also arise if the ovaries themselves are resistant or non responsive to normal levels of hormones. In addition, absent, damaged or diseased ovaries will prevent ovulation [12]. The principal symptoms associated with ovulatory disorders are: Amenorrhea, Oligomenorrhoea, Irregular menstrual cycle, Obesity, Excessive weight loss Galactorrhoea, Hirtism and Acne.[13]

2. Anatomical disorders: Disorders of the female sex organs are much more common than those of the male. This is especially true of infection and inflammatory conditions. [14]

3. Chromosomal disorders: Infertility can arise when there are abnormal chromosomes or abnormal numbers. Chromosomal aneuploidy refers to an alteration in chromosomal number from the normal diploid chromosomal complement in somatic cells or haploid complement in gametes. Chromosomal aneuploidy is the leading cause of pregnancy loss and developmental disabilities in humans. [15]

4. Unexplained infertility (Idiopathic): This is a diagnosis of exclusion.

5. Pelvic inflammatory disease (PID): Pelvic inflammatory disease (PID) is an infection of the female reproductive organs. It is a common illness. PID occurs when bacteria move from the vagina and cervix upward into the uterus, ovaries, or fallopian tubes. The bacteria can lead to an abscess in a fallopian tube or ovary. Long-term problems can occur if PID is not treated promptly.

PID can lead to serious, long-term problems: one in 10 women with PID becomes infertile. PID can cause scarring of the fallopian tubes. This scarring can block the tubes and prevent an egg from being fertilized.

Ectopic pregnancy—Scarring from PID also can prevent a fertilized egg from moving into the uterus. Instead, it can begin to grow in the fallopian tube. The tube may rupture (break) and cause life-threatening bleeding into the abdomen and pelvis. Emergency surgery may be needed if the ectopic pregnancy is not diagnosed early.

Chronic pelvic pain—PID may lead to long-lasting pelvic pain.

6. Endometriosis: Endometriosis is a disorder in which tissue similar to the tissue that forms the lining of your uterus grows outside of your uterine cavity. The lining of your uterus is called the endometrium.

7. Polycystic ovarian syndrome: Polycystic ovarian syndrome (PCOS) is one of the most common endocrine disorders in women of reproductive age. It is characterised by a combination of hyperandrogenism (either clinical or biochemical), chronic oligo/anovulation, and polycystic ovaries. It is frequently associated with insulin resistance and obesity. PCOS receives considerable attention because of its high prevalence and possible reproductive, metabolic, and cardiovascular consequences. It is the most common cause of anovulatory infertility. Ovulation induction with an aromatase inhibitor or anti-oestrogen is the first-line medical treatment. The aim of ovulation induction is monofollicular growth to avoid multiple pregnancy. The second-line treatments include gonadotrophins and laparoscopic ovarian drilling. The role and benefit of metformin in ovulation induction is uncertain. Woman with PCOS undergoing IVF are at significant risk of ovarian hyperstimulation syndrome. Women with PCOS are also at an increased risk of developing gestational diabetes, pregnancy-induced hypertension, and pre-eclampsia.

8. Advanced age, Environmental and occupational exposure to chemicals, Congenital abnormalities, Hormonal imbalance. [16,17]

The impact of the reproductive system disorders:

Female infertility may be clue to solve ovulation

problems, anatomical problems, such as fallopian tube damage or endometriosis.[18] In womb, congenital disorders, muscle tissue gland, endometriosis, polyps and adhesions can also reduce fertility.[19]The reasons for male infertility include unusual characteristics of semen, reproductive infection and disorder, erectile dysfunction or ejaculation disorder. After testing and treating each etiologic factor, couples may look for assisted reproductive technology. [18]

Endometriosis

Endometriosis is a benign estrogen-dependent inflammatory disease which develops due to the ectopic endometrial implants. Endometriosis affects more than 10%-15% of women who are of childbearing age. [18] The symptoms of endometriosis vary. Some women experience mild symptoms, but others can have moderate to severe symptoms. The severity of your pain doesn't indicate the degree or stage of the condition. You may have a mild form of the disease yet experience agonizing pain. It's also possible to have a severe form and have very little discomfort. Pelvic pain is the most common symptom of endometriosis. You may also have the following symptoms: painful periods, pain in the lower abdomen before and during menstruation, cramps one or two weeks around menstruation, heavy menstrual bleeding or bleeding between periods, infertility, pain following sexual intercourse, discomfort with bowel movements, lower back pain that may occur at any time during your menstrual cycle. The relationship between endometriosis and infertility has been mentioned in many resources. However, a cause and effect relationship is still controversial. The pelvic anatomy is deformed and fertility is decreased through mechanical adhesion, such as pelvic adhesion. These adhesions cause damage to ovule release or selection, decrease sperm motility, and causing disruption in myometrium contraction, such as fertilization disorder and embryo transfer. Infertile women are more likely to develop the disease. However, so much debate has been raised on the impact of diseases on fertility. Anti-genetic growth factors, inflammatory cytokines and normal genes are among the endometriosis-related etiologic factors of infertility.[20]

The impact of Genital Infections and Diseases

Untreated sexually transmitted infections (STIs) are among the factors that cause damage to the reproductive system of men and women. Chlamydia and gonorrhea are most common STI which lead to infertility in men and women. This disease has no symptom. Thus, it cannot be diagnosed and treated. Chlamydia causes problems for men and women. If chlamydia is left untreated, the woman will be also at risk of pelvic inflammatory disease (PID). PID is a serious condition where the upper part of the female reproductive system and its supporting structures become inflamed.[21] The studies show that pre-pregnancy diagnosis of Chlamydia trachomatis reduces the abortion caused by PID in 4 weeks. Valid evidence also shows that women with PID are at risk of ectopic pregnancy, fallopian tube infertility and chronic pelvic pain.[22] A relationship was observed between infertility and previous Chlamydia infection in women.[23] There is so much evidence indicating the relationship between trachomatis infection and any changes in semen quality. Trachoma can affect the sperm function. In vitro experiments show that C. trachomatis Tyrosine phosphorylation affects sperm proteins, causes sperm premature death and develops an apoptosis-like reaction in sperms which increase sperm surface fragmentation levels.[24]

The Impact of Age

Studies show that the risk of infertility increases with growing age.[18] Young people's knowledge of infertility is hopeful and leads to the maintenance and improvement of pregnancy health.[23]Evidence shows that age may play an important role in fertility. Pregnancy before 30 for women and before 35 for men has more chance of success. Men and women should know each other's ages that they could come to an agreement for a successful pregnancy.[25]

The Impact of Hormonal Disorders

There are many hormonal disorders that cause infertility. Hypothyroidism, hyperprolactinemia (high male hormone levels) and luteal phase defect (low progesterone) are a few examples of these disorders. Hormonal disorders are a major cause of infertility in women. The inability of women at ovulation and regulation of hormone levels leads to too high or too low production of hormones. These hormonal disorders are characterized with symptoms such as irregular menstrual cycles, excessive bleeding, or very little bleeding, pelvic and abdominal cramps, absence of menstruation or long

menstruation and excessive weight loss or weight gain. The following factors may cause hormonal disorders: gland problems such as thyroid gland, pituitary gland and hypothalamus gland problems. These preliminary glands are responsible for the production of sex hormones. Birth control pills, stress and some diseases such as hypothyroidism affect these glands. If any of these glands encounter any problem, disorder can prevent from the full process of ovulation, and thereby, pregnancy will become difficult. In addition, some treatments can cause hormonal disorders. Targeted cancer therapies can cause anatomical and hormonal changes which negatively affect the breast cancer patient's sexual potential. There are large differences in the evidence-based interdisciplinary treatment and management of breast cancer young patients who are treated and are fertile now and there are concerns about pregnancy after cancer treatment. [26]

PCOD

Polycystic ovary syndrome (PCOS) affects 5%-20% of women of reproductive age worldwide and is characterized by hyperandrogenism, ovulatory dysfunction and polycystic ovarian morphology.[27] The 2003 Rotterdam criteria are currently the internationally accepted criteria by which PCOS is diagnosed. Patients are diagnosed with PCOS when two out of three criteria are satisfied: oligo- ovulation or anovulation, clinical and/or the presence of polycystic ovaries(PCO) and exclusion of other etiologies(congenital adrenal hyperplasia and androgen secreting tumors).[28] There also exists the androgen excess and PCOS society definition which recommends that clinical or biochemical hyperandrogenism should be essential for diagnosis, but also ovulatory dysfunction is required in the form of either oligo-anovulation or PCO.[29] The pathophysiology of PCOS is multifactorial, and it is believed that a genetic predisposition exists that is exacerbated by excess adiposity. It is thought that the pathophysiology of PCOS involves the interaction between abnormal ovarian morphology, due to excess androgen production by the PCOhyperinsulinemia, and elevated luteinizing hormone (LH) levels. [30]According to the world health organization(WHO), PCOS is the commonest cause of an ovulatory infertility. Upto 70% of women with PCOS have insulin resistance meaning that their cells can't use insulin properly. When cells can't use insulin properly, the body demand for insulin increases. The pancreas makes more insulin to compensate extra insulin triggers ovaries to produce more male hormones. [31]Women with PCOS often have increased levels of inflammation in their body. Being overweight can also contribute to inflammation. Studies have linked excess inflammation to higher androgen levels.[32]

COMPLICATIONS

Many studies have been performed comparing pregnancy outcome in women with PCOS vs controls.

1. MULTIPLE PREGNANCIES: Multiple pregnancies are the most important cause of the increased perinatal morbidity observed following fertility treatments, with special regard to women with PCOS affected by an ovulatory infertility. Most of the risk of pregnancy complications is due to preterm delivery rates of multiple births.[33]

2. MISCARRIAGE: It is still debated whether women with PCOS have an increased risk of miscarriage compared to women without fertility disorder.[34]

3.PREGNANCY INDUCED HYPERTENSION AND PREECLAMPSIA:

All three meta-analysis reported 3-4 times increased risk of pregnancy induced hypertension in women with PCOS. Women with PCOS also represent 3-4 fold increased risk of developing pre-eclampsia during pregnancy.[35]

The Impact of Smoking and Alcohol Consumption

Meta-analyzes have shown that 40% of infertile men are smokers.[18] Chemicals (such as nicotine, cyanide and carbon monoxide) in cigarettes cause a rapid destruction of ovules. Unfortunately, ovules cannot be replaced if destroyed. It means that female smokers experience menopause one to four years sooner. The number and quality of sperm decrease in male smokers; sperm mobility is reduced and the number of sperms with abnormal appearance increases. Smoking may make the sperm unable to fertilize eggs.[36] Female smokers do not get pregnant like non-smoking women. Infertility rate in male and female smokers is almost double the infertility rate in non-smoking women. The reproductive risk increases with the daily number of cigarettes. Even

fertility treatments such as in vitro fertilization (IVF) may not be able to completely eliminate the effects of smoking on fertility. During IVF, female smokers need more drugs to stimulate ovulation and have fewer ovules. Female smokers have 30% lower chance of pregnancy through IVF method compared to non-smoking women. [26] Alcohol consumption in men reduces sperm count; and motility and number of normal morphology sperm in them.[18]

The Impact of Immune Responses

Immunological mechanism plays an important role in sexual problems, such as recurrent miscarriage (RM) (three or more RSA), infertility and implantation failure. This shows that successful pregnancy depends on the maternal immune response to the growing semi-allogeneic fetus.[37] Embryo implantation is affected by local and systemic immune responses including immunoglobulins, cytokines, and hormonal and endometrial factors. Contribution of these factors to the success of implantation and pregnancy is critical. Natural killer cells play an important role in female sexual function. This cells are correlated with inductive failures, NK cell cytotoxicity induced abortion or infertility and gene expression. [38]

The Impact of Mobile Phone

Use Mobile device emits radio frequency electromagnetic waves that can reduce sperm quality and disrupt the normal function of the body. There are many real mechanisms emphasizing the impact of mobile phones on sexual ability of men. All these mechanisms rely on the impact of mobile phones on biological system, such as thermal and non-thermal effects. Since testicles are a shallow organ, it may absorb the radiant energy more than other organs. Oxidative stress (OS) developed in testicles because cell phones cause free radicals in sperm. OS is a major cause of infertility in men. [39]

The Impact of Sexual Violence

The literature shows that the history of sexual violence is associated with infertility. The psychological trauma caused by sexual violence leads to ovulation infertility or sexual dysfunction. Infertile women had experienced sexual violence three times in their lives compared to fertile women. Although the relationship between sexual violence and fallopian tube infertility could be easily explained, this relationship with any infertility other than fallopian tube infertility is vague and confusing. This may be due to the fact that fallopian tube pathology was diagnosed using human chorionic gonadotropin (HSG) against laparoscopy as a gold standard method. HSG is an unreliable test for tube openness with an intensity of 62% and sensitivity of 83%. Therefore, non-tubal infertility group includes an unknown number of undetectable tubal infertility.[40]

The Impact of Anxiety

Although the impact of anxiety on male infertility has not been clearly proved, the incidence of such problems in the lives of men may cause anxiety. Once faced with their infertility, men may have excessive stress, including the anxiety related to power, masculinity, and sexual adequacy. The anxiety may decrease the intimacy between partners and avoid the sexual behaviour. [41]

The Impact of Obesity

According to the researchers, obese women, especially women with abdominal fat hardly become pregnant and have low chance of infertility treatment. In women with a body mass index (BMI) >25, compared with BMI <25, the pregnancy rate is lower (respectively, 10.5% vs. 253%). The role of obesity in pregnancy focuses on the physiology of fat body and metabolic disorders. [36] Articles show that nearly 10% of sub-fertile or infertile women have been diagnosed with diminished reduced ovarian (DOR). [43] Polycystic ovary is one of the common reasons of ovulation disorder in women of childbearing age. [44] Some studies have shown that usually 30%-70% of women with PCOS are obese. Overweight and obesity in women with PCOS exacerbates the severity of androgen and disorders metabolic profile.[45]

The impact of Diseases That Can Cause Infertility

Systemic lupus erythematosus (SLE) is a multiple automatic system that affects fertility in women and men. Genital tract in women and men may be affected by cytotoxic treatment due to the disease activity. Fertility disordermay be due to the problems which prevent from successful fertilization and thus lead to infertility, avoid

the effective implantation in the uterine wall and cause problems in maintaining pregnancy after implantation and complications during childbirth. [46] Varicocele is a pathological enlargement of the pampiniform venous plexus in the scrotum that affects testicular function and can lead to infertility. However, the pathophysiological mechanism that leads to varicocele infertility is not fully understood. The following five mechanisms seem to contribute to the impact of varicocele on testicular function, reduced blood flow leading to hypoxia, thermal stress, oxidative stress, hormonal imbalance and detoxification.[47]

The Impact of Nutrition

Although no definitive relationship was discovered, selection of supplements or food groups is crucial before and during pregnancy attempt to improve fertility in women and men.[48] A high saturated fat diet is associated with reduced sperm quality. Changes in diet over the last decades may partly explain the high frequency of abnormal sperm count. Decrease in saturated fat intake in general and reproductive health benefit.[49] Lower sperm concentration and total sperm count are correlated in men with saturated fat diet.[18]

Unknown Factors

There are numerous factors affecting infertility and nature has multiple roles in this fact. The special impact of some of these factors on fertility is still uncertain and unclear. The relationship of these factors with fertility in humans remains unclear and further research is required in this regard.[25]

HORMONES IN INFERTILITY

ROLE OF HCG IN REPRODUCTION

The glycoprotein hormone family is believed to share similar structural features and the structure of hCG has been elucidated.[50,51] The a- and h-subunits each have remarkably similar folds. When the heterodimer is formed, the single loop of one subunit lies adjacent to the double loops of the other subunit. The h-subunit of hCG has six disulphide bonds and the a-subunit has five. The crystal structure revealed that the previously defined disulphide bonds could not all be made.[52,53] These disulphide bonds appear to play an integral role in maintaining the heterodimeric structure. These structural features, together with the observation that the individual subunits are inactive, have implied that the quaternary structure provided by the assembly of the a- and h-subunits is important for hCG function. However, work with genetically fused a- and h-subunits have shown that the heterodimeric configuration is more important for assembly and secretion than for biological activity.[54-56]hCG is heavily glycosylated with the carbohydrate content accounting for 30% of its molecular weight. There are two asparagine linked carbohydrate chains on each subunit and the carboxyl terminus of hCG has four O-linked glycosylation sites. The O-linked oligosaccharides extend the life of the hormone in the circulation. If the unique C-terminal extension of hCG bearing these oligosaccharides is added to FSH, then the in vivo half life of the hormone is increased.[57] The Asn-linked carbohydrates may also be of importance in the folding and correct disulphide bond arrangement of hCG.[58] The glycosylation status of the free a-subunit and hCG varies throughout pregnancy, with hCGa becoming more highly branched and both hCGa and hCG more fucosylated as gestation progresses.[59] These carbohydrates prevent association of the a- and h-subunits, and the free a-subunits are linked to prolactin secretion.[60,61]

FSH

FSH is synthesized and secreted by gonadotropins in the anterior pituitary gland; it is a glycoprotein that regulates the development, growth, pubertal maturation and reproductive processes of the human body. In females, it initiates follicular growth, specifically affecting granulose cells. With the concomitant rise in inhibin B (a complex protein that down regulates FSH synthesis and inhibits its secretion). FSH levels then decline in the late follicular phase. This seems to be critical in selecting only the most advanced follicle to proceed to ovulation. [62]

LH

LH is produced also by the anterior pituitary gland; it is a glycoprotein and essential for reproduction. In females, at the time of menstruation, LH initiates follicular growth, specifically affecting granulose cells. [63]

Testosterone

Testosterone is a steroid hormone from the androgen group. It is the principal male sex hormone, produced by testes in men and by thecal cells of the ovaries and placenta in women. Testosterone is also synthesized by zona reticulais of the adrenal cortex in both sexes. In general, Testosterone has both anabolic and virilizing effects.[64,65]

Prolactin (PRL)

Prolactin is mainly synthesized in the pituitary gland and involved in many different biological functions including behavior, immunology, endocrinology, metabolism and reproduction. [66] More than (300) different biological functions have been attributed to PRL, the major ones being induction of differentiation and growth in mammary epithelia and stimulation of milk protein secretion[67] PRL is secreted mainly by lactotrope cells, breast deciduas and immune system. [68] Hyperprolactinemia is one of the most common endocrine disorders of the hypothalamic pituitary axis. It is more commonly diagnosed in women than in men and if it persists, it usually causes infertility, amenorrhea, galactorrhea, oligomenorrhea, hyperandrogenism, hirsutism, acne, regular menses; but with anovulatory cycles.[69]

Conclusion

Infertility is a difficult process to overcome, but dealing with infertility is instrumental to pursuing a positive family building journey in the future. Social stigma due to infertility is seen in many cultures throughout the world in varying forms, when women cannot conceive the blame is put on them, even when 50% of infertility issues come from man. The effect of infertility can lead to social shaming from internal and social norms surrounding pregnancy, which affects women around the world. Many infertile women tend to cope with immense stress and social stigma behind their condition, which can lead to considerable mental distress. The long term stress involved in attempting to conceive a child and lead to emotional distress that may manifest as mental disease. Present review concludes that treatment and self-care significantly improves the chances conception which includes:

Hormone treatments, fertility drugs, timed intercourse, medications like estrogen, anti-diabetic medications and sex hormone suppression improves the chances of conception

- Eat balanced and nutritious diet with plenty of fresh fruits and vegetables.
- Treating or preventing existing diseases such as diabetes and hypothyroidism.
- Regular physical examinations help to detect early signs of infections or abnormalities.
- Do not delay on parenthood

Ethical Clearance- Nil

Source of Funding- Nil

Conflict of Interest- Nil

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