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FEMALE INFERTILITY: A REVIEW ON DEFINITION, CAUSES AND ITS TREATMENT.

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Abstract: A fertility is a capability of childbearing. The women losses fertility due to some conditions such as endometriosis, PCOS anovulation, genital tuberculosis, tubal diseases which results into infertility. Infertility is the condition in which as the inability of getting pregnant after trying for at least 6-12 months of regular unprotected intercourse. Approximately 8-10% couples are affected by infertility problem. In India almost 27.5 million people are suffered by this problem. It is multidimensional problem with social, economic and cultural implications. Infertility may be used with sterility with only sporadically occurring spontaneous pregnancies. The increase in prevalence of infertility is due to at least four factors: delayed childbearing, alterations in semen quality due to habits such as cigarette smoking and alcohol and changes in sexual behavior. The aim of this study was to perform a systematic review of the literature to determine which factors are responsible for infertility in females and how possible to do with this problem and clinically relevant treatment.

***Index Terms* – Subfertility, Causes of infertility- Anovulation, PCOS, Endometriosis, Genital TB, Treatments of infertility- Laparoscopy, IVF, GIFT& ZIFT, Hormonal treatment**

I. INTRODUCTION

Childbearing and raising of children consider one of the most important events in the human's life. it is accepted that giving birth to baby and raising of child is most important responsibility of parents and it is associated with their goals of completeness and happiness. As compared with other species of animal kingdom, human's fertility rate is unfortunately low.

Fertility is the natural capability of childbearing or to produce offspring. Women loses their fertility because of some kind of problems like ovulatory disorders, obesity etc. and somehow this is called infertility [1].

Infertility is the inability of getting pregnant after trying for at least 6-12 months (if a woman is 35 or older) of regular unprotected intercourse. According to WHO, about 8-10% of couples are facing to infertility problems. In India, about 27.5 million of couples are suffer from infertility, while in US almost 12% of population facing the same problem of infertility. In past, people had little control on their fertility but who were not capable to give birth to child had no other option, they just accepted this fact. But today, infertility is a common problem in couples worldwide, and medical science having some strong solutions on that problems.

TABLE 1: Published definitions of infertility: [4]

ORGANISATION	DEFINATION
National Institute for Health and Clinical Excellence guidelines 2004	Infertility should be defined as to conceive after regular unprotected sexual intercourse for two years in absence of known reproductive pathology.
ASRM 2008	Infertility is disease defined by failure to achieve a successful pregnancy after 12 months or more of regular unprotected intercourse. Earlier evaluation and treatment may be justified based on medical history and physical findings and is warranted after 6 months for women over age 35 years.
International Committee for Monitoring Assisted Reproductive Technology (ICMART) and World Health Organisation 2009[c]	Infertility (clinical definition): a disease of reproductive system defined by failure to achieve a clinical pregnancy after 12 months or more of regular unprotected sexual intercourse
Demographic definition	Inability of a non-contracepting, sexually active woman to have a live birth

SUBFERTILITY:

In some cases, infertility is some degree of subfertility in which about 1 in 7couples needs specialist advice who help them to conceive. Subfertility is any form of reduced fertility with prolonged time of unwanted non-conception [3]. Infertility may be used only with sometimes occurring spontaneous pregnancies. The major factor affecting the spontaneous pregnancy is the time of unwanted non-conception which determines the grading of subfertility.

Subfertility is of two types: Primary and Secondary. Primary subfertility is the delay for a couples who have no previous pregnancies. While Secondary subfertility is the delay for couples who have conceived previously but the pregnancy may not have been successful, for example, miscarriage (or spontaneous abortion, is an event that results in the loss of fetus before 20 weeks of pregnancy), ectopic pregnancy (occurs when the fertilized egg implants and grows outside the uterus) [4].

The cumulative probabilities of fertile couples to conceive are generally age independent. The cumulative probabilities of conception declines with age because of the heterogeneity of fecundity increases [5]. The natural cumulative conception rate in 35 to 39 years aged women is around 60% at one year while 85% at 2 years. As longer as a couple has to conceive, they have as smaller as the chances of spontaneous conception. A couple has conceived 1.7 times more than the couples who are trying for longer, if the duration of subfertility is less than 3 years [6].

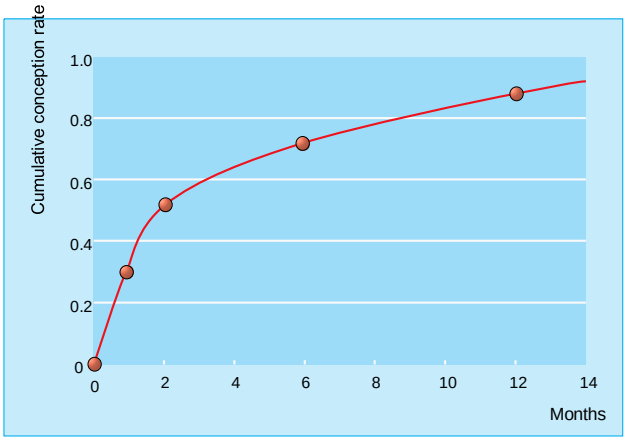

FIGURE 1: Cumulative conception rate in the first year of trying

Sexual response cycle is the most important cycle to promote the fertility because it comprises physical and emotional changes in the body. Normally in physiology, the two gonadotropin hormones, follicle stimulating hormone (FSH) and luteinizing hormone (LH) are produced in pituitary gland and their secretion is controlled by gonadotropin releasing hormone (GnRH) which is released by hypothalamus [3]. As new cycle starts, the hypothalamus releases GnRH which acts on pituitary glands to secrete FSH and LH. These two hormones stimulate the ovary and development of follicle occurs. In response to FSH about 30-40 follicles grows every month but only one mature egg releases every month. The mature follicle releases estrogen which is produced by inner lining of follicles, when this egg is ripe. The high amount of estrogen stimulates pituitary gland to release more amount of LH leading to LH surge. LH acts on mature follicle and causes rupturing of it to release the mature egg in the ovary i.e. ovulation [3]. Major causes of infertility are ovulation disorders, male factors (including disorders of spermatogenesis and obstruction), tubal damage, unexplained factors and other causes includes endometriosis and fibroid.

II. CAUSES OF INFERTILITY IN WOMEN:

A woman needs ovaries, follicles and uterus in a good condition for healthy pregnancy, if any one of them getting affected by some problems or not properly working can leads to infertility. So, there are many problems or causes leads to infertility are listed below:

2.1 ANOVULATION:

Anovulation is the condition in which the development and rupture of follicle is not occur and hence the oocyte from the follicle does not released. This occurs for about 30% of infertility and is present with absence of periods i.e. amenorrhea and also with irregular periods i.e. oligomenorrhoea. Sometimes anovulation can be treated with medical or surgical inductions [10]. Also, there are many treatments over anovulation which are simple and effective so, couples may have very contact with doctors for their advices. In some cases, anovulation may be derived from one of the following conditions:

- **Hyperprolactinaemia:**

Hyperprolactinemia can be defined as the presence of abnormally high level of prolactin in the blood in the body od woman. Normal level of prolactin is about 10-35 ng/ml (1ng ≅ 21.2 mU/ml). Prolactin secretion shows circandian rhythm, it secrets in higher concentration in night while in low concentration during day time. The regulatory mechanism of prolactin is independent on sleep, it depends on hypothalamic regulator and on pituitary melatonin secretion [11].

The high level of prolactin which is observed during pregnancy and lactation leads to hyperprolactinemia and it can be present as pathological condition at any stage and its excessive release of prolactin caused by:[11]

TABLE 2:

Dysfunctions	Mechanisms
Idiopathic	Impaired hypothalamic dopamine secretion
Adenoma, hypothalamic stalk interruption	Disruption of dopamine delivery and/ or secretion of prolactin
Acromegaly	Prolactin secretion from GH adenoma
Primary hypothyroidism	Increased hypothalamic TRH
Poly cystic ovary syndrome	Raised estrogen concentration

Also, the elevated prolactin level results from some substances such as digestive medications, anti-depressants, neuroleptics, hypotensive drugs, as well as stressed conditions, excessive exercise, high protein intake, chest trauma, surgery and sexual intercourse etc [6].

The study of thyroid functions is necessary in every woman who is affected by hyperprolactinemia, because of hyperthyroidism usually occurs due to elevated concentration of prolactin [11].

- **Hypogonadotropic hypogonadism:**

Hypogonadotropic hypogonadism is the rare disease which is characterized by low level of follicle stimulating hormone and luteinizing hormone. This condition expressed with estradiol concentration of about < 40 pg./ml this condition can be idiopathic and seen in weight disorder and excessive exercise. It is caused by hypophyseal and hypothalamic dysfunction [6].

2.2 POLY CYSTIC OVARIAN SYNDROME (PCOS):

Poly cystic ovarian syndrome is the common metabolic and reproductive disorder in the women of reproductive age [12]. It is heterogenous disorder and it is characterized by hyperandrogenism and chronic anovulation [13]. It is defined as the endocrine disorder which causes enlargement of ovaries with small cysts on their outer edges. Polycystic ovarian syndrome is also known as Stein-Leventhal syndrome. The exact cause of polycystic ovarian syndrome is not known, but it is primarily characterized by some combinations of signs and symptoms of androgen excess and ovulation dysfunction. According to diagnostic criteria, the women affected by polycystic ovarian syndrome is ranging about 6-20% of their reproductive age [13].

In 2003, the European Society for Human Reproduction and Embryology and American Society for Reproductive Medicine redefined PCOS in presence of 3 features: (1) Oligo or chronic anovulation, (2) biochemical and / or hyperandrogenism, (3) Ultrasonographic evidence of PCOS [14].

Rotterdam and AE-PCOS Society criteria recognize at least 3 phenotypes:

1. Frank PCOS (Oligomenorrhea, hyperandrogenism and PCOS),
2. Ovulatory PCOS (Hyperandrogenism, PCOS and regular menstrual cycles),
3. Non-PCO PCOS (Oligomenorrhea, hyperandrogenism and regular ovaries).
4. Mild or norm androgenic PCOS (Oligomenorrhea, PCOS and normal androgens) [14]

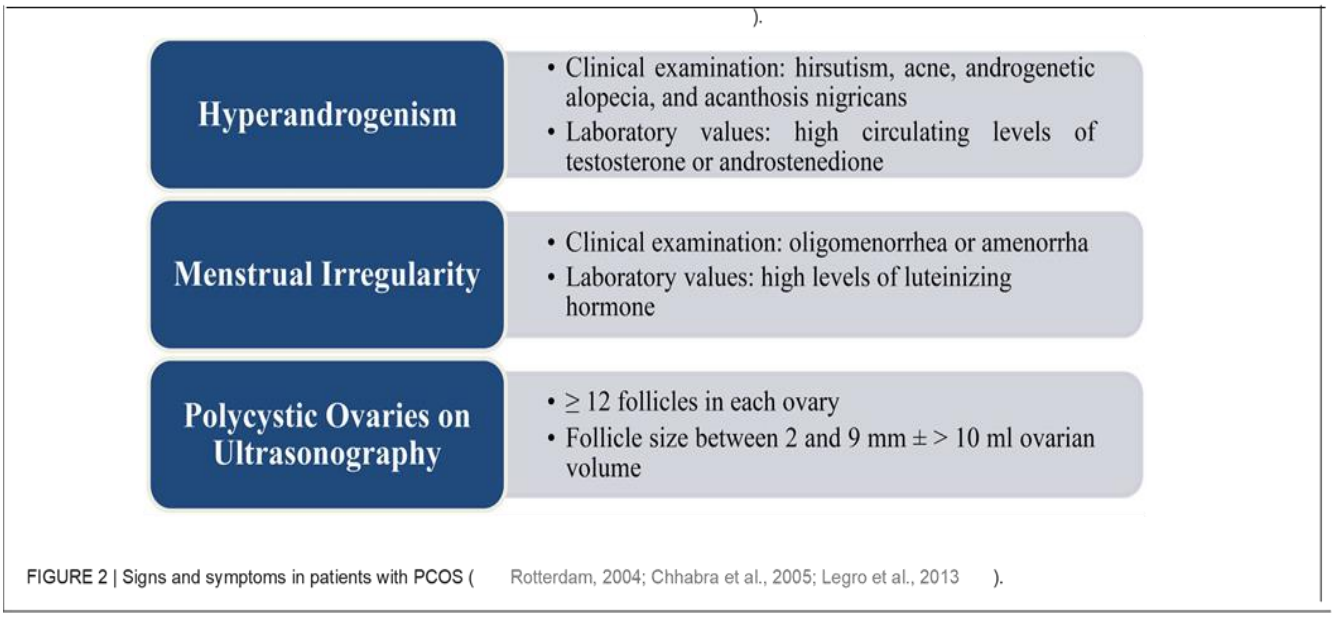

FIGURE 2 | Signs and symptoms in patients with PCOS (Rotterdam, 2004; Chhabra et al., 2005; Legro et al., 2013).

Pathophysiology of PCOS:

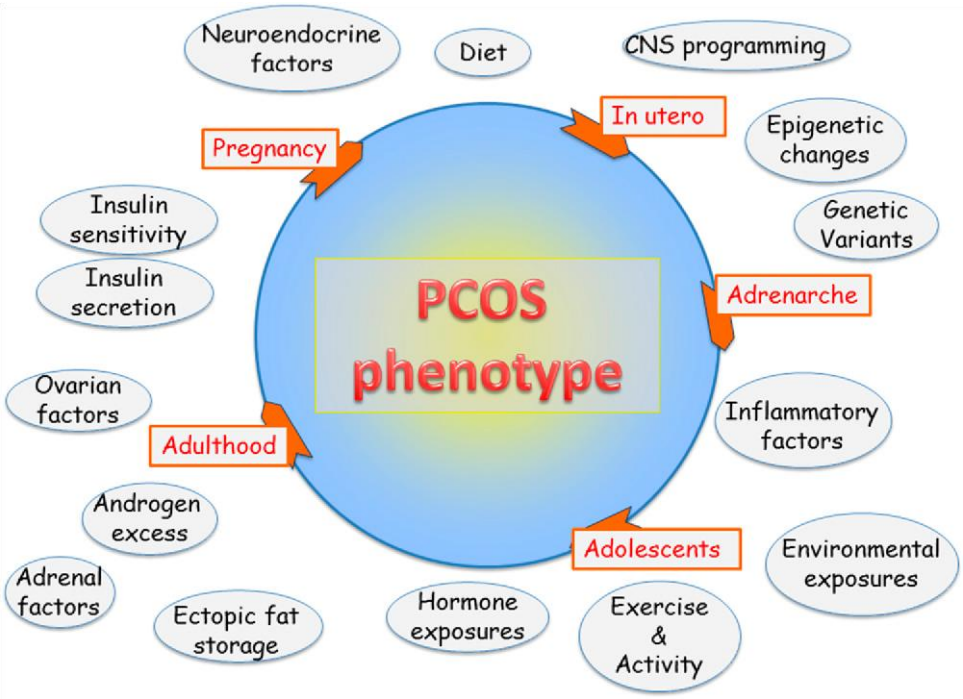

FIGURE 3: Factors contributing to PCOS phenotype. The factors potentially affecting pathophysiology of PCOS are shown in the circle. Not all factors affect to each individual [13].

- **Ovary, Adrenal and Androgen excess:**

PCOS is characterized by excessive ovarian secretion or adrenal androgen secretion. Some factors which are contribute to the excessive ovarian androgen production- (1) intrinsic factors such as altered steroidogenesis, and (2) extrinsic factors to the ovary such as hyperinsulinemia. Distortion interactions an=mong the endocrine, paracrine and autocrine factors which are responsible for follicular maturation. The follicular maturation can be contributing to the dysregulation of ovaries in PCOS [13].

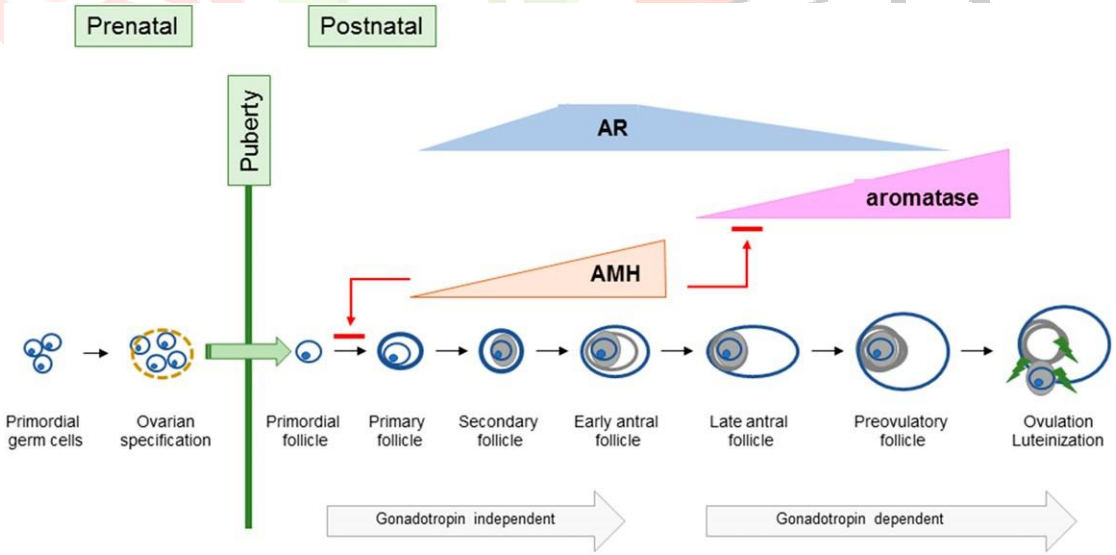

FIGURE 4: Ovarian follicle development during developmental periods [13].

- **Neuroendocrine factors:**

Increased LH pulse frequency, LH pulse amplitude, and increased LH/FSH ratio are described in women with PCOS. Hypothalamic neurons in the nucleus secretes kisspeptin, neurokinin B, and dynorphin. These neurons labelled as KNDy neurons, and are competitors for the hypothalamic GnRH pulse regulators because of the localization of these three peptides and their roles of episodic GnRH secretion. LH and FSH pulse frequencies are modulated by GnRH pulse frequencies. Increased GnRH pulse frequencies increases LH pulse frequencies while decreases FSH pulse frequencies [13].

- **Valproic acid (VPA) and Hypothalamus-pituitary ovarian (HPO) axis Functions:**

Valproic acid is a branched short-chain fatty acid. It is used to treat epilepsy, bipolar disorders, and to prevent migraine headaches. VPO interferes with GABA degradation pathways to increases the GABA levels. GnRH neurons expresses both $GABA_a$ and $GABA_b$ receptors, that are implicate GABA signaling for GnRH secretions. The women who are treated with VPA can develops PCOS-like symptoms. The women with PCOS indicated increased LH pulse amplitude and LH pulse frequency on frequent blood sampling. These clinical observations suggest that GABA signaling can influence neuroendocrine changes which are associated with PCOS such as LH pulse frequency [13].

- **Insulin resistance, Hyperinsulinemia and β cells:**

The insulin resistance, compensatory hyperinsulinemia and hyperandrogenism are included in the phenotype of female patients with insulin receptors gene mutations. Insulin receptor gene mutations are very rare in the women with PCOS, although insulin resistance and hyperinsulinemia are commonly observed in women with PCOS. Insulin is a hormone which is responsible for the glucose homeostasis and lipogenesis. It also shows its effects on carbohydrates, fats and protein metabolism. Insulin acts as mitogenic hormone and its actions are mediated by insulin receptors and these receptors are found in numerous tissues of the HPO axis [13].

2.3 ENDOMETRIOSIS:

Endometriosis is one of the most common, chronic and benign gynecological conditions. Although some women are asymptomatic while most women have pelvic pains, infertility or an adnexal mass. Endometriosis is defined as the presence of endometrial glands and stroma outside the uterine cavity. It is a condition that affect to women in reproductive period which is an estrogen-dependent chronic inflammatory condition and may associated with pelvic pains and infertility [15].

It is also characterized by ectopic endometrial implants and these implants typically occurs in pelvic region but also have been seen in upper abdomen, peripheral and axial skeleton, lungs, diaphragm and central nervous system [16]. The common sites of endometriosis are ovaries, broad ligaments, uterosacral ligaments, uterus fallopian tube, sigmoid colon and appendix. It is the disease that severely affect the women in age of about 25-35, because the growth of implants is depend on ovarian produced steroids [16].

The prevalence of endometriosis is up to 10-15 % in reproductive aged women. But the prevalence of endometriosis increases to 25-50 % in women with infertility and 30-50 % of women with endometriosis have infertility [16]. In women who undergo tubal sterilization, the prevalence of endometriosis is 1-7%, while in women who undergoing laparoscopy for evaluation of infertility, the prevalence of endometriosis is 9-50 %. The prevalence of endometriosis ranges from 30-80 % among women with pelvic pains [17].

TABLE 3: Common symptoms endometriosis and their rate of occurrence: [19]

Dysmenorrhea	60-80%
Chronic pelvic pain	40-50%
Deep dyspareunia	40-50%
Infertility	30-50%
Severe menstrual pain and irregular flow or premenstrual spotting	10-20%
Tenesmus, dysphasia, haematochezia, costiveness, or diarrhoea	1-2%
Dysuria, pollakiuria, micro or macroscopic haematuria	1-2%

Other symptoms of endometriosis are pains and heavy feeling in lumbo-sacral column or legs, also nausea, lethargy, chronic fatigue, hemoptysis, scapular or thoracic pain, and acute abdomen. The severity of symptoms and probability of diagnosis of endometriosis increases with age [17].

The relationship between endometriosis and infertility is debated from many years. Fecundity is in the range of 0.15-0.20 per month in normal couples and it is decreases with age while it is in the range of 0.02-0.10 monthly in untreated women with endometriosis and infertility [18]. Fecundity is defined as the natural capability to produce offspring. The lack of fertility is infertility and the lack of fecundity is sterility. The endometriosis causes infertility or decreases in fecundity is remains controversial [18].

There is no correct mechanism which explain the link between endometriosis and infertility. However, several mechanisms have been clarified it but none of these mechanisms have been proved to decrease the fecundity in the women. These several mechanisms are distorted pelvic anatomy, altered peritoneal function, altered cell mediated and hormonal function, endocrine and ovulatory abnormalities and impaired implantation [18].

The pelvic anatomy distortion is the so-called pelvic factor which readily explain the infertility in patients of endometriosis. Major pelvic adhesions disturb the tubo- ovarian liaisons and it can impair oocyte release from ovary or inhibit ovum pick-up or its transport [19].

The growth and inflammatory behavior of ectopic endometrial implants which is modulated by a complex network of cellular and humoral immunity factors can affects to the embryo implantation. The increased volume of peritoneal fluid with a high concentration of activated macrophages, prostaglandins, interleukins, tumor necrosis factor and proteases are present in the women with endometriosis. The peritoneal fluid contains ovum capture inhibitor which is responsible for fimbriae of ovum capture. And because of these alterations some adverse effects occur on the functions of oocyte, embryo, fallopian tube and sperms [19].

The levels of IgG, IgA and lymphocytes are increased in the endometrium of women with endometriosis. Because of these elevated levels the alterations occurred in endometrial receptivity and embryo implantation. Autoantibodies to endometrial antigens are also increased in some women with endometriosis [18, 19]. The endocrine and ovulatory disorders may occur in women with endometriosis, including luteinized unruptured follicle syndrome, impaired folliculogenesis, luteal phase defect, and premature or multiple luteinizing hormone surges [19].

Some authors suggested that some changes in receptivity in endometriosis may affect to the uterine implantation. Endometrial dysfunction occurred due to delayed histological maturation or biological disturbances [17]. Deceased fecundity was observed in the women with endometriosis is because of disorders of endometrial dysfunction. Endometrial expression of the αvβ integrin (a cell adhesion molecule) is reduced in some women with endometriosis during the time of implantation. Also, in some women with endometriosis, there

is presence of very low level of enzyme involved in the synthesis of endometrial ligand for L-selectin which is a protein that coats the trophoblast on the surface of blastocytes [19].

The presence of ectopic endometrial tissue may be related with functional disorders of eutopic endometriosis. Abnormal uterine contractions occur due to cascades of biochemical product like prostaglandins which released in pelvic structures after irritation and inflammation. The abnormal uterine contractility may interfere with adhesion and subsequent penetration of embryo on the predecidulised endometrium. The process of endometrial shedding may be controlled by the uterine contractility at the time of menstruation, transport of gametes, conception, implantation and maintenance of ongoing pregnancies. Abnormal uterine contractility may be associated with some medical entities like dysmenorrhea, endometriosis, and infertility [19].

2.4 GENITAL TUBERCULOSIS:

Tuberculosis one of the oldest and serious infectious bacterial disease that affects to the lungs in humans. Female genital tuberculosis is rare in some developed countries and is a very frequent cause of pelvic inflammatory disease and infertility. In India about 40% of population is affected by TB. In 1993, the TB declared as 'Global Emergency' by WHO [20]. It tremendously affected on reproductive health and is etiological factor in 30% of cases of infertility. In 2008, about 9.4 million cases i.e. equivalent to 139 cases per 100,000 individuals are affected by TB globally [20]. Most of the cases occurred in Asia about 55% (mostly in India, China and Indonesia) and in Africa of about 30% (mostly in south Africa and Nigeria), also in Eastern Mediterranean region (7%), European region (5%), and American region (3%). It is estimated that about 5-10% of infertile women affected by tuberculosis and this rate is <1% in United States while 13% in India [20]. More than 20% of all TB cases are Extra-pulmonary tuberculosis, since the Human Immunodeficiency virus is pandemic [21].

Genital TB cases are less than 50% among all genitourinary cases. The age of women that affected by genital TB is in the range of 20-40 years in developing countries while in Western Societies it is seen in that women who are over 40 years [21]. The reason behind this difference in age between developing and developed countries has not yet completely clarified but still it is proposed this is related to the younger age at marriage or childbearing in developing countries while older age to childbearing in developed countries. It is again becoming a major problem in the whole world due to expanding pool of immunosuppressed individuals that mostly affected by HIV, and due to the development of drug-resistant tuberculosis [22].

TABLE 4: Genital organs and their rate of occurrence of genital TB [24]

Organs	Rate of occurrence
Tubes	90-100%
Uterus	50-60%
Ovaries	20-30%
Cervix	5-15%
Vagina/ vulva	1%

Female genital TB is always secondary tubercular lesion and is a form of extra-pulmonary TB that affects female genital organs like fallopian tube (most commonly affected; 90%), endometrium (50%) and ovaries (10-30%) [22]. Primary infection of genital organs is hematogenous and it is rarely transmitted by sexual intercourse. Organisms like *M tuberculosis hominis* or *M. tuberculosis bovis* are not only responsible for genital TB, as many atypical varieties of bacteria are being isolated. Genital TB in women usually present with infertility, chronic lower abdominal or pelvic pains, menstrual dysfunction (oligomenorrhea, amenorrhea, or postmenopausal bleeding), abnormal vaginal discharge and abdominal masses.

TABLE 5: Symptoms and their rate of occurrence: [22]

Symptoms	Rate of occurrence
Adhesions, tubercles and hyperaemia	59.6%
Pelvic adhesions	48%
Tubercles	33.8%
Lessons on bowel/ omentum	25.4%
Adhesions in pouch of Douglas	11.3%
Encysted effusion	8.45%
Unilateral adnexal mass	11.3%
Bilateral adnexal mass	22%

Other symptoms: amenorrhea, vaginal discharge, abdominal swelling and symptoms with fistula formation are less frequent; uterovesical, tubovesical, tubointestinal and tuboperitoneal fistulae; vague lower abdominal discomfort; also, general malaise, undue fatigue, low-grade fever [24].

2.5 TUDAL DISEASE:

Fallopian tubes are highly specialized organs and their role is transporting and picking up eggs, transporting sperm and embryo. The fallopian tubes are necessary for egg fertilization and sperm capacitation. The tubes are also important in nutrition and development because the egg is fertilized in fallopian tubes and the first stage of development of embryo occur during its journey to the uterine cavity. Fallopian tubes are vulnerable to infection and surgical damage by affecting to fimbriae or highly specialized endosalpinx which may impair their functions. Almost 12-30 % of infertile couples are affected by fallopian tube obstruction [25].

Tubal disease may involve proximal, distal or whole tube. Pelvic inflammatory disease is a most common cause of tubal damage, of about more than 50% cases, and it may affect to the fallopian tube at many places [26]. Pelvic inflammatory disease (PID) is a spontaneously occurring infection of uterus and fallopian tubes. Pathogenic organisms are the most important factors in acute pelvic inflammatory disease like *Neisseria gonorrhea* and *Chlamydia trachomatis*, and mycoplasma, endogenous aerobic and anaerobic bacteria are less pathogenic. Bacteria are present in the vagina in high concentration of about 10^5-10^9 colonies per mm while in cervix in low concentration [27].

Around 50% cases of pelvic inflammatory disease are affected by *Chlamydia trachomatis* and it is spread through sexual transmission. Chlamydial infection is asymptomatic or have less signs of infection, hence it is not easily diagnosed. Symptomatic as well as asymptomatic infections both can damage to reproductive tract. It is commonly spread by direct extension along the mucosal surface from cervix to endometrium [25]. Obstructions occurred by tubal damage are due to immune-mediated fibrosis and have immunopathologic basis. In seroepidemiologic study, the women affected by tubal infertility had a distinctive immunodominant immune response to 57 kilodalton Chlamydial antigen. And this study of immune-response to the antigen in women with Chlamydia salpingitis may help to define the reason of developing tubal obstruction in some women infected by *C. trachomatis* [28]. They may cause urethritis, cervicitis, endometritis and salpingitis which then resulted peritubal adhesions. These adhesions can cause subfertility / infertility, ectopic pregnancy and chronic pelvic pain [25].

Gonococcal virulence is important for pelvic inflammatory disease. It contains pili, fine hair-like protoplasmic projections which provides attachment to epithelial cells of cervix and fallopian tubes. Virulence factor that produced by gonococci of an endotoxins that damages fallopian tubes in the absence of living organism [27]. It is common in young and urban women of low socioeconomic groups and in people who have several sexual partners. It is a localized infection of lower genital tract, invasive infection of upper genital tract, or disseminated disease with systemic manifestations, sometimes it may be asymptomatic [25].

2.6 PREMATURAL MENOPAUSE:

Premature menopause is the menopause that occurs before the age of 40 years, while early menopause is refers to menopause that occurs at or before the age of 45 years. Premature or early menopause occurs spontaneously or it can be induced. If it is induced then it may be due to either medical interventions like chemotherapy or surgical interventions like bilateral oophorectomy (is a surgery to remove both fallopian tubes and ovaries) [29]. The average age at natural menopause has been estimated at between 50-51 years but recent population-based study of 45-54 years old women estimated that more than 85% of non-hysterectomized women will undergo natural menopause by age 55 [30]. The average age at natural menopause is defined as the women's age at last menstrual period before stopping menstruation for 12 consecutive months.

Premature Ovarian Failure (POF) is also known as Primary Ovarian Insufficiency (POI) or Primary Ovarian dysfunction (POD). It is a syndrome of amenorrhea, low sex steroid levels, and increased gonadotropin levels in women who are younger than 40 years. It is mostly idiopathic but sometimes caused due to autoimmune disorders, genetic causes, infections or inflammations enzyme deficiency or metabolic syndrome. POF affected to the women about 1% in the age of under 40% and spontaneous early menopause is affected to women of about 50% to women in the age of 40-45 years [29]

Bone density, early onset osteoporosis and fractures, impaired endothelial functions, earlier onset of coronary heart disease, increased cardiovascular disease, and total mortality are at increased risk in the women with premature spontaneous menopause [29]. Women with Premature Ovarian Failure has been estimated to have more anxiety, depression, somatization, sensitivity, hostility and psychological distress than the women with normal ovaries. Premature Ovarian Failure is associated with autoimmunity and hence the women with autoimmune Premature Ovarian Failure are at high risk of adrenal insufficiency, hypothyroidism, diabetes, myasthenia gravis, rheumatoid arthritis and systemic lulus erythematosus [29].

Induced menopause may cause due to premenopausal bilateral oophorectomy or from cancer treatments like chemotherapy and radiation therapy [29]. Ovarian damage by chemotherapy is depend on the age of treatment and the type of treatment. Ovarian failure is at low risk for women in younger age than 40 years than older age women but the exposure to higher dose of alkylating agents and high doses of radiations to the ovaries may induce to ovarian failure [29]. Induced menopause is reported from bilateral oophorectomy with serious consequences like premature death, cardiovascular and neurological disease, osteoporosis, menopausal symptoms, psychiatric symptoms, and impaired sexual functions [29].

Another one of the strongest risk factors for menopause is smoking. The women who smoke are at high risk to undergo natural menopause about 1 year earlier than non-smokers [30]. Tobacco smoke contains polycyclic hydrocarbons which may be toxic to ovarian germ cells and may leads to estrogen deficiency to follicular exhaustion. The alkaloid components of tobacco smoke contain nicotine and anabasine may lower estrogen levels [30]. Tobacco smoke also cause preferential shift of 2-hydroxylation over 16-hydroxylation of estrogen in smokers leads to less active estrogen. Effect of smoking on hypo-thalamic-pituitary function may also possible. Hence, smoking affects to average age at natural menopause by lowering the estrogen levels [30].

Both sporadic ovulation and occasional pregnancy may occur with Primary Ovarian insufficiency [31]. Up to 50% of women are affected by Primary Ovarian Insufficiency, among them 25% are occasionally ovulated, while 5-10% are conceived and get delivered. The incidence of Primary Ovarian Insufficiency may increase with age, women with age <20,30 and 40 years affecting about 0.01%, o.1% and 1% respectively [31] The symptoms of Primary Ovarian Insufficiency are amenorrhea, oligomenorrhea, menometrorrhagia, infertility, symptoms of estrogen deficiency, including hot flashes, vaginal dryness, sleep disturbances, sexual dysfunction, and cognitive decline [31].

2.7 UNEXPLAINED INFERTILITY:

Approximately 30% of infertile couples have unexplained infertility, defined as normal test results in the basic tests for ovulation, sperm production, and fallopian tube patency [32]. The female partner's age is one factor that does con-tribute to the unexplained category; when a woman older than 37 years is the only reason for infertility, test results are likely to be normal [32]. Although couples with unexplained infertility have normal basic diagnostic test results, the mean prognosis for a live birth is 30% to 35%, similar to the mean prognosis for infertility with known causes. The initial treatment of unexplained infertility is 3 to 6 cycles of clomiphene citrate and IUI [32].

III. TREAMENTS OF FEMALE INFERTILITY:

3.1 LAPROSCOPY:

The laparoscopic technique is used for the treatment of anovulatory infertility in women with Polycystic Ovarian Syndrome. The patients who did not responds to any hormonal medication were successfully treated by wedge resection of the ovaries but this involves laparotomy [33]. It is estimated that the laparoscopic ovarian diathermy is effective alternative to wedge resection. Laparoscopic ovarian diathermy was preferable to wedge resection as it does not require laparotomy [33]. Laparoscopy is performed under general anesthesia with endotracheal intubation [33].

The diagnostic laparoscopy provides direct visual access to inner pelvic anatomy without restoring to major abdominal surgery. It is performed in post menstrual phase under general anesthesia [34] All patients which are undergoing to this procedure are investigated properly for blood count, blood urea, blood sugar, urine examination, ECG, chest x-ray, husband's seminogram, basal body temperature, luteinizing hormone monitoring, endometrial biopsy and ultrasonography. The chromotubation was carried out in almost all cases of infertility and it is used to test the patency of tube under laparoscopic vision by using 10-15 ml of o.5 % autoclaved methylene blue dye [34].

The laparoscope was introduced subumbilically and trocar and cannula were introduced into iliac fossae for forceps used to hold the ovarian ligament and and for diathermy probe. After inspection of pelvic organs methyl blue was instilled through cervix to check tubal patency [33]. Then normal saline was introduced into the pouch of Douglas to increase ovarian cooling after diathermy. Each ovary was lifted to anterior surface of uterus to minimize the damage to other neighboring viscera during unipolar diathermy applied using the special probe. After that each ovary was put into the pool of saline. The probe has 8mm central spike which is covered with insulated solid cone of maximum 6 mm diameter [33]. This spike penetrated into the ovarian capsule with the aid of short burst of diathermy and it prevent the probe from slipping on the surface of ovary. The diathermy was used for 4 seconds to each ovary 8 times in 3 cases, 6 times in 1 case, and 4 time in 16 cases and 4 time in 1 case to one ovary in which another ovary cannot be visualized because of adhesions. Endometrial biopsy usually taken to remove endometrial abnormalities [33].

The use of laparoscopic multi-electrocauterization is proposed by Gjoannaess in 1984 for the treatment of PCOS. Ovulation was resumed, even after the period of contraceptive use following electrocauterization and pregnancy was obtained in few months. Hence electrocauterization is used primarily for treatment of PCOS undergoing laparoscopy [35]. Cauterization was performed in 1987 by using small scissors and by this 8-10 punctures are made on ovary with current of 4 amp until the penetration of cortex is occurred. After 3-4 days of laparoscopy, there is decrease in aldosterone, testosterone, estradiol and LH is observed in women with PCOS. Also, follicle stimulating hormone level is increased [35].

Laparoscopic laser drilling was introduced and it was used for the treatment of PCOS within past 15 years [35]. Laser provides the controllable power density, desirable depth of penetration, predictable thermodamage of surrounding tissue and also diminish the risk of adhesions. Types of laser used are carbon dioxide, argon, YAG. With this YAG about 3-5 drillings are made on each ovary. In 1989, some different type of laser model is performed on women with PCOS and were poor responders to clomiphene [35]. The ovarian vaporization was performed by using argon, CO_2 or potassium titanyl phosphate (KTP) laser, during laparoscopy. Two puncture techniques are used to drain all small visible subcapsular follicles of each ovary and drill randomly placed craters in ovarian stroma. The use of laser gives greater control on the type of damage induced in the ovary and this is not appearing to translate into clinical advantage [35].

Laparoscopic ovarian drilling can achieve single ovulation without risk of ovarian hyperstimulation and multiple pregnancies [36]. This method is an alternative option to gonadotropin administration in anovulatory women with PCOS who are resistance to clomiphene citrate. The risk of laparoscopic ovarian drilling is small and includes the development of adhesions and destruction of normal ovarian tissues. Also, there is possibility of damage to the ovary but it is limited [36]. This technique is performed by only well-trained physicians and it is not used for any other indication except infertility.

3.2 IN VITRO FERTILIZATION:

In vitro fertilization (IVF) is a treatment of unexplained infertility. In IVF, the multiple matured eggs are retrieved from women and eggs are fertilized with men' sperm outside the womb and in the laboratory. Then fertilized embryos are implanted in the uterus after fertilization of 3-5 days [37]. The mild and moderate endometriosis affects the quality of oocytes aspirated from women recovered by treatment of IVF by reducing fertilization rate [37]. The therapy for women with PCOS is the indication of ovulation by clomiphene citrate. After the use of gonadotropin therapy, the major complication of ovulation induction is the occurrence of 10% multiple pregnancy rate [38]. The induction of ovulation with exogenous gonadotrophin therapy was replaced by ovarian stimulation and IVF. IVF is suggested in some cases like tubal damage, severe endometriosis, preimplantation genetic diagnosis and male factor infertility [38].

Severe stimulation protocol is used for the treatment of women with PCOS undergoing IVF, including clomiphene citrate associated with human menopausal gonadotropins (hMG), human menopausal gonadotropin alone, GnRH agonist associated with hMG or recombinant FSH, recombinant FSH alone, and GnRH antagonist associated with hMG or recombinant FSH [38]. According to the recent analysis, the cycle cancellation rate is increased and the duration of stimulation is elevated in the women with PCOS, even when the daily dose of FSH is similar to that women without PCOS. The main complication of ovarian stimulation is the occurrence of ovarian stimulation syndrome [38]. Although this treatment is helpful to many infertile couples, but it has not a major impact on overall success with infertility treatment, because of inability to access it [39]. Less than 10% of couples undergo IVF because of high cost of its technically advanced procedures [39].

3.3 GAMATE INTRA-FALLOPIAN TRANSFER (GIFT) AND ZYGOTE INTR-FALLOPIAN TRANSFER (ZIFT)

Zygote intra-fallopian transfer (ZIFT) is an advanced form of embryo transfer in which the fertilized and dividing embryo is carefully transferred to fallopian tube during laparoscopy. This is very different from GIFT and it seems a better option. It is used for the treatment of long-standing non-tubal infertility for 2 years of period. Devroey et al. performed the first successful use of ZIFT in humans [40]. It can be performed only in women who have at least one potent fallopian tube. In ZIFT technique, two laparoscopic procedures are to be performed – one is for oocyte collection while another is for embryo transfer [41]. The other form of ZIFT is tubal embryo transfer (TET).

The GIFT was developed as a form of therapy for infertile patients. GIFT is a technique where gametes (an egg and sperm) are transferred into a woman's fallopian tubes via a laparoscopic procedure [41]. This technique was first introduced in the 1980s and seemed to show promise for unexplained infertility. It requires at least one healthy fallopian tube and is not suitable in severe male factor infertility. Some couple choose GIFT for religious or moral reasons because the egg is not fertilized outside the body [41]. However, this is a drawback of GIFT because fertilization cannot be con- firmed. Sometimes, surplus eggs are fertilized in the lab for subsequent freezing. If there is a

good rate of fertilization in the lab eggs, then fertilization is also assumed to have taken place in the fallopian tubes [41]. However, a successful pregnancy is the only definitive proof. Indications for GIFT include:

Indications for GIFT include: [41]

• Pelvic adhesions unrelated to pelvic inflammatory disease

• Endometriosis

• Cervical factor infertility

• Oligo-anovulatory infertility

• Unexplained infertility

• Religious or social reasons

Contraindications for GIFT include:

• Pelvic inflammatory disease

• Tubal infertility

• Severe male factor infertility

• Contraindications for laparoscopy

Success rates of GIFT vary, depending on the underlying causes of subfertility and the patient's age, with average pregnancy rates per embryo transfer about 30%.27 [41].

3.4 HORMONAL TREATMENT:

Endometriotic lesions have been shown to have an increased production and decreased inactivation of estradiol. This is due, in part, to abnormal expression of both aromatase and 17-beta hydroxysteroid dehydrogenase [16]. Common medical therapies used to treat symptoms of endometriosis such as pelvic pain, dyspareunia and dysmenorrhea target ovarian estrogen production. Medications used as endometriosis therapy are hormonal medications including combined oral contraceptives, progestins, danazol and gonadotropin-releasing hormone agonists or antagonists (GnRH analogues). Although these medications may help treat pain, they have shown no benefit in the treatment of endometriosis-associated infertility [16].

OCP are the most commonly used medications for the long-term treatment of women with PCOS. By suppressing the hypothalamo-pituitary-ovarian axis, OCP decrease LH secretions, increase sex hormone binding globulins, and decrease free testosterone levels. This addresses hyperandrogenism-mediated symptoms improving acne and hirsutism, corrects menstrual cycle abnormalities, and provides a mean for effective contraception [12].

Clomiphene citrate (CC) is one of the most frequently prescribed ovulation drugs. It is used in women who do not ovulate or ovulate infrequently, for example, in PCOS patients [40]. CC has been used to induce ovulation in IVF patients. CC works by making the pituitary gland secrete more FSH. This encourages more follicles to develop. The usual dose of CC is 50–100 mg, but doses up to 200 mg can be prescribed in women who fail to respond to standard doses [40].Women who do not ovulate because of hypothalamic disorders or have very low estrogen levels should not be prescribed CC. t has been suggested that, in the long term, CC injures Yin and may exacerbate Heat symptoms in patients who have pre-existing Heat Syndrome, especially Liver Heat [40].

The contribution of insulin resistance to anovulation in PCOS led to the introduction of insulin-sensitizing drugs in an attempt to restore ovulation and enhance pregnancy. Of the insulin-sensitizing drugs, metformin has been the most widely studied in PCOS and has the most reassuring safety profile [42]. Metformin, a biguanide, has been used for over six decades as an oral antihyperglycemic agent in the treatment of diabetes and is therefore particularly helpful in patients with PCOS who are insulin-resistant. Since then the literature on metformin in PCOS has suggested improvement in fertility such that, by lowering insulin levels, metformin may restore the hormonal milieu required for ovulation to occur. Metformin has no serious side effects in otherwise healthy young women, does not increase the risk of multiple pregnancies or ovarian hyperstimulation syndrome (OHSS), and is reasonably well tolerated except for gastrointestinal symptoms, which are less troublesome with the new slow- release preparations [42].

IV. SUMMARY:

- The aim of this study was to addressed the exception and apprehension in connection with pregnancy, birth.
- It seems fairly clear that infertility researchers have begun to apply insights from the sociology of health and illness, the sociology of gender, the sociology of the body and the sociology of deviance to understanding.
- The literature described here sends a clear message about the how infertility matters to the women life.

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