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Reproduction Failure in Females: An Overview of Plausible Factors

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Abstract

Considered as one of the major baffling disorders, reproduction failure in females is widespread with intensifying occurrence but mysterious etiology. A number of factors for reduced pregnancy success have been reported, some of which are preventable or cured by targeted intervention while others remain untreatable. The impact of these factors on reproductive capacity may differ depending on individual etiology and circumstances. Keeping this in consideration, the present article reviews the existing data regarding the potential factors affecting female reproductive health.

Introduction

Reproduction is a multifaceted, irreversible process that involves a hierarchy of distinct and essential events comprising formation and maturation of gametes, transport of male gamete in female tract, fertilization, implantation, decidualization, placentation and lastly delivery of issue i.e. parturition [1]. Any anomaly in the normal course of this dynamic process can lead to infertility. It is medically defined as failure to conceive within one year despite well-timed sexual intercourse without the use of birth control agents [2]. It is well acknowledged fact that factors responsible for infertility are equally distributed amongst males and females. However, the disease outcome in the society is shaped by patriarchy. The women are at the receiving end of the psychosocial anguish and emotional turmoil [3]. Thus, determining the causes responsible for reduced conception in females has become new Holy Grail in field of reproduction [4]. With this brief background, the present review was written with an aim to summarize various factors leading to female infertility.

Causes of Female Infertility

Infertility in females is multi-etiological disease emanating from platter full of conditions arising due to anomalies in major organs *viz*. ovary, fallopian tubes, endometrium, cervix or vagina of female reproductive tract. These factors may act alone or under certain circumstances, they may coexist. They lead to defects in reproductive tract making it unfit for fertilization or, if it does happen, normal implantation and development of placenta becomes unfeasible [5].

Ovarian disorders

Ovarian disorders represent a critical cause of infertility. The most common ovarian disorders, which are associated with infertility, are anovulation, ovulation with luteal insufficiency and luteinized non-ruptured follicle syndrome (LUF).

Anovulation

Anovulation, a primary cause of female infertility, is defined as a condition in which a woman does not produce an egg during her menstrual period. It accounts for about 25-50% of female infertility cases [6]. It is a heterogeneous disease with a number of underlying causes and frequently presented with irregular periods (oligomenorrhoea) or complete absence of periods (amenorrhoea). The etiology of anovulation may be attributed to increased age, unhealthy lifestyle and endocrinopathy like Poly Cystic Ovarian Syndrome (PCOS).

The literature is not ambiguous about the threat of increasing age to altered fertility. In pursuit of better career or financial stability to quench the materialistic desires and easy availability of safe and effective contraceptives, women often postpone conception. Unaware of the fact that their biological clock is ticking, they are putting the inherent desire to have children into danger [7]. The female fecundity is at zenith in early and mid-twenties. The age-related dwindle in fertility starts at the age of 32 with a drastic decrease after the age of 37. Referring back to the development of female reproductive system, it is documented that in female fetus, proliferation of germ cell reaches to a state of dormancy by 20 weeks, as a result of which a female being born consists of about 5 million primordial follicles. By menarche, this number decreases to approximately 500,000. The reduction in primordial follicles because of follicular atresia/apoptosis continues with every menstrual cycle and reaches about 25,000 at the age of 37 and 1000 near to menopause and sometimes women may reach the state of complete sterility even before menopause [8]. Further, obstetrics enigmas may also follow enhancing age.

Another important factor responsible for anovulation is lifestyle followed by individual. Lifestyle factors are behaviors and circumstances that are, or were once, modifiable and can be a contributing factor to decrease the rate of conception. Major lifestyle factors that are linked to anovulation include obesity and smoking. Obesity is known to have profound negative impact on reproduction as evident by a positive correlation between increased body mass index with lower rates of pregnancy and live births and increased chances of miscarriage [9]. Cigarette smoking, either active or passive, is also linked to increased rates of infertility, reduced ovarian response to hyper stimulation, enhanced chances of spontaneous abortion, ectopic pregnancy, tubal infertility, lower clinical pregnancy and intrauterine growth retardation in comparison to nonsmokers [10,11]. A number of different mechanisms have been put forth, by which smoking can harm the reproductive system in females [12]. Chemicals (nicotine, cyanide and carbon monoxide) present in

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cigarettes can lead to demolition of ovules. Since, ovules cannot be restored; therefore, the damage becomes permanent [13,14]. Besides, smoke also exerts negative impact on oocytes: thicker ZP and higher frequency of chromosomal abnormalities. However, there is less data available with regard to influence of cigarette smoke on ovulation number and oocyte morphology [15].

Polycystic Ovarian Syndrome (PCOD) is a major gynecological endocrinopathy characterized by the combination of hyperandrogenism and anovulation with ball shaped ovaries with cysts. With an incidence rate ranging from 5%-13% in childbearing age, it accounts for about 80% of anovulatory infertility cases [16]. PCOS is a multifaceted disorder that emerges because of deformities in the hypothalamic-pituitary axis, steroidogenesis (Higher levels of testosterone and dehydroepiandrosterone) and insulin resistance (Genetic factors leads to hyperinsulinemia, which in turn increases the release of androgens). The major symptom is excessive release of androgen within the ovary, which causes the formation of huge numbers of tiny preovulatory follicles that are non-responsive to the normal amounts of follicle stimulating hormone [17]. Thus, a principal follicle is hardly produced.

Ovulation with luteal insufficiency

Luteal phase insufficiency, a state of ovarian dysfunction, is one of the major causes of implantation failure and has been held liable for irregular menstrual bleeding, miscarriages and abortive assisted reproduction. Ever since Georgiana Seegar Jones first introduced this condition into the medical world, it has been a hot topic of discussion amongst the research groups in the area of reproductive endocrinology. It has been estimated that luteal phase insufficiency accounts for 3-20 % of infertile patients and 50-60 % of patients with recurrent pregnancy loss [18].

In natural cycle, luteal phase is defined as the period between ovulation and onset of either pregnancy or menstrual cycle. Following ovulation, the formation of corpus luteum occurs which further releases steroid hormones i.e. estrogen and mainly progesterone [19]. An ideal synchronized signal between embryo and endometrium allows the successful implantation of embryo, subsequently; developing blastocyst releases Human Chorinic Gonadotropin (HCG), which in turn helps to sustain function of corpus luteum [20]. In case pregnancy occurs, corpus luteum under the influence of LH produced by pituitary gland continues to secrete progesterone for 7 weeks after which the placenta takes over. Progesterone produced by corpus luteum aids not only in maintaining pregnancy, but also controls uterine contractibility and cervical competence which further contributes to ideal pregnancy. However, in a state of luteal insufficiency, progesterone production by the corpus luteum is not adequate to maintain endometrium and early pregnancy. Thus, implantation of embryo does not take place, which results in infertility. The well-documented causes of ovulation with luteal insufficiency are dysfunctional corpus luteum, insufficient duration of progesterone secretion and abnormal endometrial response to progesterone.

Luteinized Unruptured Follicle syndrome (LUF)

LUF is lesser acknowledged cause of female infertility even though a higher incidence of LUF syndrome in infertile women has been documented in various studies. It was first reported by Jewelwicz (1975) who demonstrated that well developed follicles could remain unruptured despite luteinization similar to normal menstrual cycle [21].

During the course of regular ovulation process, following a rush of luteinizing hormone the follicle ruptures and releases egg, which is transported to fallopian tube and uterus for fertilization, conception and implantation. However, in case of LUF syndrome there is a failure of an ovum to be expelled from the ovary into the fallopian tube. The follicle fails to rupture, thereby, retaining the oocyte within the ovary. There itself, follicle grows to full maturity, undergoes luteinization and start producing progesterone. In this anomaly, all other parameters linked to pregnancy such as normal menstrual period and biphase of basal body temperature, secretory alterations in the vaginal mucus and progesterone levels are regular with ovulation. However, an ovum is not released into tubes [22].

While the exact cause of LUF syndrome is still unidentified, it has been suggested that the utilization of Nonsteroidal Anti-Inflammatory Drugs (NSAIDs) in the periovulatory phase and endometriosis could result in LUF syndrome [23,24].

Endometriosis

Endometriosis is an enigmatic and debilitating, estrogen-dependent condition, which was first reported by a German physician, Daniel Shroen. It is a medical condition that arises when the endometrial lining of uterus starts growing outside of it and attaches to various organs in pelvic region, particularly, the ovaries and fallopian tubes [25]. The prevalence rate of endometriosis in infertile women is documented to be 20-55% in comparison to 5-10% in the fertile females. In some women it leads to formation of lesions that can cause severe pain and scarring while in others may not present any symptoms at all [26].

The existing vision today is that endometriosis can interfere with fertility in many ways [27,28]. Several pathomechanisms that have been proposed to explicate endometriosis-linked infertility are based on amount, type, and location of endometriotic lesions i.e. present in the ovaries, fallopian tubes or uterus. Endometriosis if extends to the ovaries, results in enhanced number of inflammatory cells in the fluid of peritoneal cavity thereby, leading to formation of cysts or endometriomas. Inflammation because of existence of endometriomas can cause altered ovulation and oocyte production [29]. In cases where endometrial lesions are present in fallopian tubes, the major function of tubes i.e. gamete transport is affected. It has been postulated that inflammatory milieu and elevated cytokine levels in endometriosis impairs tubal function and reduces tubal motility. Anarchic myometrial contractions linked with endometriosis can also mess up with gamete transport. In addition, endometriosis may also affect uterus, thereby altering the endometrial receptivity and causing implantation failure [30].

To sum up, in cases of intense endometriosis, infertility in woman may occur as a result of mechanical obstruction of the sperm-egg interaction by adhesions, endometriomata, and pelvic anatomy malformations. On the other hand, in women with non-severe forms of endometriosis reactive oxygen species may play pivotal role, which encourage the growth of endometrium into peritoneal cavity, thereby, resulting in anatomical changes, which could lead to infertility [31].

Tubal factor infertility

Tubal factor infertility is characterized by occlusion in one or both of the fallopian tubes that is responsible for 30-35% of cases in which a female fails to procreate [32]. Fallopian tubes play an important role of capturing the oocyte after ovulation, providing of suitable milieu for movement of spermatozoa for fertilization of the oocyte and finally successful transportation of the embryo to uterine cavity for implantation. Tubal abnormalities that interfere with any of these actions consequently result in infertility [25]. Tubal pathologies have been recognized as the underlying factors contributing to both primary and secondary infertility; however, the incidence is higher in cases of secondary infertility.

The most common form of tubal factor infertility is microbial infections induced Pelvic Inflammatory Disease (PID). Depending upon the severity of infection, absolute blockage of tubes may occur or mild intraluminal adhesions may be formed. Oocyte capture by the fallopian tube may also be inhibited as a consequence of immune response generated against microbial infections that can lead to formation of adhesions on the fimbrial end which thwart the movement of spermatozoa or embryo. The microbes can also damage the ciliated cells which prevent transport of embryo, thus leading to tubal occlusion [33].

Another imperative factor in case of tubal pathologies is scar tissue formation because of pelvic or tubal surgery. The scar tissue can affect the fallopian tubes thus impairing its ability to pick up and transport the egg. Al Subhi et al. [34], while assessing the risk factors for infertility, reported that previous pelvic surgeries were considerably higher in infertile patients. Besides surgeries, endometriosis could also lead to scar tissue formation that involves fallopian tubes. The use of hormonal contraceptives containing progesterone may also lead to tubal factor infertility. Progesterone has been reported to reduce ciliary movement and tubal smooth muscle contraction ensuing decreased ciliary beat. Intrauterine devices are also considered as risk factor for tubal infertility as it paves a passage for ascension of microorganisms into upper genital tract [35].

Uterine anomalies

A number of congenital and acquired uterine anomalies, which have been reported in literature, are well acknowledged to cause female infertility. The exact impact on fertility is decided by the anomaly under consideration. These anomalies can be congenital or acquired.

Congenital uterine anomalies

Congenital uterine anomalies are uterine malformations arising due to defect in any step during the mullerian ducts development [36]. They are held guilty for increased incidences of sterility, recurrent abortions, intrauterine retardation and fetal death, premature delivery, fetal malposition, and retained placenta. The development of uterus and uterine tubes occurs from mullerian ducts in the sixth week of gestation through three different phases i.e. organogenesis, fusion, and septal resorption [37]. Any defect in these phases may result in incidence of innate uterine disorders. The major congenital uterine disorders, according to the American Fertility Society [38], are: Class I: uterine hypoplasia and agenesis; Class II: unicornuate uterus; Class III: uterus didelphys; Class IV: bicornuate uterus; Class V: septate uterus; Class VI: arcuate uterus; and class VII: diethylstilbestrol-related anomalies Class I: Mullerian agenesis is an abnormality that is characterized by innate lack of the vagina and variable uterine development [39]. The uterus is generally absent; though 7-10% of women may have an underdeveloped uterus with functional endometrium. Class II: Unicornuate uterus: It represents an asymmetrical lateral fusion defect, wherein, one cavity of uterus is completely normal along with a fallopian tube and cervix, however, the other side demonstrates disrupted development. The unicornuate uterus may be divided into four different types on basis of the status of the rudimentary horn: a) communicating, b) non-communicating, c) no cavity, d) no rudimentary horn present [40]. Class III: Uterus didelphys: Uterus didelphys is a condition, which arises due to absolute failure of two mullerian ducts to fuse thereby resulting in cervix duplication along with the uterus. Though this duplication is limited to the uterus and cervix, however, it may also extend to vulva, bladder, urethra, vagina and anus. It is a symptomatic condition wherein patients turning up for evaluation are presented with obstructed vagina [41,42]. Class IV: Bicornuate uterus: Bicornuate uterus, the most frequent uterine abnormality, is corollary of curtailed fusion of the müllerian ducts, resulting in alteration in separation of the uterine cavities. When present in mild form, a minor midline septum is formed with a negligible fundal cavity groove whereas in the extreme cases complete internal division of uterus occurs down to the cervix leading to absence of communication between uterine cavities. Class V: Septate uterus: It is an anomaly in the final phase of development, wherein the resorption of the central septum between the two uterine cavities was supposed to occur. In such situation, the fusion step is normal thus allowing the formation of normal-appearing uterine surface, but, there is abnormality in resorption of the internal septum. It can be complete or incomplete with presence or absence of a longitudinal vaginal septum. Class VI: Arcuate uterus: The arcuate uterus is characterized by the slight midline septum with a wide fundus, rarely with small fundal cavity notch. Amongst the uterine anomalies, obstetrical complications are minimum in case of arcuate uterus [43]. Class VII: Diethylstilbestrol-related anomalies: Diethylstilbestrol (DES), is a synthetic estrogen, which was initially used against pregnancy related complications. However, in utero exposure to DES can also result in uterine abnormalities.

Acquired uterine abnormalities

Acquired uterine anomalies are the abnormalities in uterus that develop after birth. The major causes of these types of anomalies can be indirect trauma (previous dilation and curettage, and uterine surgery), direct trauma or a therapeutic abortion. Endometrial carcinoma, cervical carcinoma, and gestational trophoblastic diseases further add to the etiology of acquired uterine anomalies [44]. The acquired uterine anomalies that increase the likelihood of female infertility are polyps, fibromas, adenomyosis, endometrial hyperplasia and intrauterine adhesions [45]. Polyps are symptomatic benign contained overgrowth of glands, blood vessels, and stroma in uterine cavity because of increased age, hypertension, overweight, and tamoxifen use. Uterine fibroids, myomas or leiomyomas, are asymptomatic noncancerous outgrowths on the muscular wall of uterus. Being asymptomatic, they often go unnoticed. Only in cases they turn out to be big enough, fibroids hinder the implantation of embryo on the uterine lining thereby leading to premature pregnancy

loss. The precise root of this growth is still unidentified; however, genetics basis and female hormones are speculated as the causative agents [46]. Three main kinds of uterine fibroids that have been documented are Subserosal, intramural and submucosal. Subserosal fibroids are the type of fibroids, which have been reported to grow into the abdominal cavity i.e. outside of the uterus. They are generally asymptomatic. Intramural fibroids are those that are contained in the uterus i.e. initiate and grow within the uterine wall. They can negatively alter fertility and increase the chances of loss of pregnancy. Submucosal fibroids are the rarest in occurrence but extensively involved in causing infertility. They also grow inside the endometrial cavity of uterus. Adenomyosis is another benign condition, described by growth of endometrial glands into the uterine myometrium. The origin of this condition can be traced to uterine trauma, abortion, chronic endometritis, and hyperestrogenism. Endometrial Hyperplasia is a disease characterized by atypical proliferation of endometrial glands, an outcome of which is thickened endometrium. Excessive secretion of estrogen is reported to be the source of endometrial hyperplasia. Intrauterine adhesion, popularly known as uterine synechiae, is defined as a condition of occurrence of fibrotic tissue in the endometrial cavity, resulting in intra cavity adhesions. It is acquired as a consequence of injury to endometrium usually following infection [47].

Cervical anomalies

Cervical mucus is a major determinant of transport of spermatozoa to uterine cavity and fallopian tube. An insufficient quantity or poor quality of cervical mucus may prevent fertilization and accounts for about 10% of female infertility cases [48]. A number of factors may alter cervical mucus in a negative way. Hormonal fluctuations in the course of menstrual cycle, hormonal dysfunctions such as inadequate estrogen release and/or premature increase in progesterone may alter the secretion and composition of mucus that may lead to decreased sperm penetrability eventually resulting in infertility. Medication can also negatively affect mucus receptivity of spermatozoa. Chronic cervicitis, acute inflammation and cystic fibrosis are also held culpable of reducing cervical mucus receptiveness.

Another condition that is also clinically relevant in cases of infertility in women is cervical stenosis, which is medically defined as narrowing of cervix thereby leading to obstruction of menstrual flow. Infertility in this situation is because of the failure of spermatozoa to travel to the upper genital tract. This disorder may be congenital or acquired (infection or trauma). It may also be an obstacle in the path of assisted fertility techniques such as embryo transfer and intrauterine insemination [49]. Cervical polyps, the small finger-shaped structures originating from the surface of the endocervical canal, are one of the most frequently encountered benign cervical lesions in females that interfere with reproduction process [50]. Cervical atresia, a rare abnormality, may manifest itself with primary amenorrhea and cyclic pelvic tenderness because of hematometra and retrospective menstruation. However, booming pregnancies is possible, but it is often accompanied by increased risk of ascending tract infection. Lastly, the presence of anti-sperm antibodies in cervical mucus may also affect sperm motility in cervical mucus.

Vaginal anomalies

A number of vaginal anomalies or conditions occurs which alter the reproductive outcome. Firstly, Gartner's duct cysts, developed after menarche, obstruct the menstrual flow resulting in dysmenorrhea, pelvic pain, or a pelvic mass. Secondly, congenital lack of the vagina, Mayer-Rokitansky-Kuster-Hauser syndrome, is the outcome of the termination of mullerian duct development. Thirdly, the complete, imperforate transverse vaginal septum resulting from incomplete fusion of the vaginal components of the mullerian ducts and the urogenital sinus represents one of the rare aberration of female genital tract. The complete septum can cause accumulation of menstrual blood consequently leading to hematocolpos and hematometra whereas incomplete septum permits partial flow of menstrual blood and such individuals complain of dysmenorrhea and dyspareunia [51].

Apart from anatomical factors, other important vaginal factor contributing to infertility is inefficient neutralization of vaginal pH at time of sexual intercourse. As sperm motility and viability is maintained at neutral pH, failure to neutralize acidic pH may be detrimental for spermatozoa [52].

Genitourinary tract infections

Infections tend to have a profound negative impact on general health and if present in genitourinary tract, they may play a decisive role in deciding the likelihood of conception in females. The lower genital tract is open to a huge microbial load, whereby microorganisms can march into upper genital tract *via* the mucosa or the epithelial layer [53]. They can effortlessly involve various anatomical and urogenital sites of female reproductive system such as vagina, cervix, uterus and fallopian tubes. They can act at any step *viz*. production of reproductive cells, transport of male gamete to the oocyte, fertilization and implantation of embryo, of normal fertility process [54]. Thus, in case of genitourinary tract infections, negative effect on human fertility is chiefly attributed to direct damage to the genital tract mucosa by microorganisms by initiation of pro-inflammatory reaction of the host thereby leading to atypical pelvic inflammatory disease and hence, tubal factor infertility [55,56]. Another plausible way is indirect influence of microbes on functions of the organs of reproductive tract such as ciliary motility in fallopian tube [57,58]. Moreover, the cross-reactivity between microbial and host results in formation of antisperm antibodies, that also adds to the etiology of microorganisms induced infertility [59,60]. Another mechanism of infertility has been given by Pelzer et al. [61], wherein they reported that the microorganisms themselves or products of their metabolism present in follicular fluid or in uterus may also impair the FSH from binding to its receptor, thereby, leading to implantation failure. Since, movement of spermatozoa in female genital tract to meet oocyte is a major determining factor, hence, damage to spermatozoa by different microorganisms may be another risk factor for infertility. Sperm damage can be induced by direct adherence of the microorganism to the sperm surface or by the metabolic products released by these microorganisms [62-66].

Conclusion

There are various well-established and speculative factors that play a pivotal role in infertility. Despite extensive research in field of factors responsible for infertility, etiology of around 30% of infertility cases remains unexplained. Thus, there is need of empirical research in this field that would provide insights into the mechanism of

idiopathic infertility and will pave a way towards the new treatment interventions, thereby, bringing women out of the burdens of psychosocial trauma.

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