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A review of Female Infertility; important etiological factors and management

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ABSTRACTS

The difficulty to conceive or subfertility constitutes a major social and psychological burden amongst couples especially in African women. In Nigeria, it is estimated that female factors and unexplained infertility generally accounts for 50-80% of cases of infertility and thus the need to review the various works done by researchers. In this review the contributions of the different etiological factors in female infertility was looked into and attempt was made to update the available information on the management of female infertility. The main aim of this review is to generate information which could act as guideline in the evaluation of female infertility. From the reviewed studies on female infertility it is concluded that a loss of 5-10 % of body weight in obese anovulatory infertile women, maintenance of a healthy lifestyle, prevention and prompt treatment of sexually transmitted diseases and not delaying parenthood are amongst the purported good preventive measures to tackle infertility amongst infertile women.

Key words: Female infertility, hypothyroidism, anovulation, hyperprolactinemia,

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INTRODUCTION

Infertility is the inability of a couple to achieve pregnancy over an average period of one year (in a woman under 35 years of age) or 6 months (in a woman above 35 years of age) despite adequate, regular (3-4 times per week), unprotected sexual intercourse [13]. Infertility may also be referred to as the inability to carry a pregnancy to the delivery of a live baby. Infertility can be due to the woman, the man, or both; primary or secondary. In primary infertility, the couples have never been able to conceive; while in secondary infertility there is difficulty in conceiving after having conceived (either carried the pregnancy to term or had a miscarriage). Secondary infertility is not present if there has been a change of partners within the one year period, which has its associated peculiar chances to be infertile.

Cervical infertility (CI) involves inability of spermatozoa to get to the uterus due to damage to the cervix or cervical factors such as cervical stenosis [53]; antisperm antibodies [18]; inadequate, hostile or non-receptive cervical mucus [17], and cervical infections from sexually transmitted diseases (Chlamydia, gonorrhea, trichomonas, mycoplasma hominis and ureaplasma urealyticum).

Epidemiology

Infertility is a complex disorder with significant medical, psychosocial, and economic problems [57]. Data from population - based studies suggest that 10-15 % of couples in the world experience infertility [16]. In Africa, its prevalence is particularly high in sub-Sahara ranging from 20% to 60% of couples [43]. It is estimated that female factors and unexplained infertility accounts for 50-80% while the male factor accounts for 20-50% of the cause of infertility in different parts of Nigeria [15].

Available evidence suggests that the social consequences of infertility are particularly profound for African women as compared to men [28]. Community based data suggest that up to 30 per cent of couples in some parts of Nigeria may have proven difficulties in achieving a desired conception after two years of marriage without the use of contraceptives [2].

RISK FACTORS AND CAUSES

Infertility may be caused by an underlying medical condition that may damage the fallopian tubes, interferes with ovulation, or causes hormonal complications. These medical conditions include pelvic inflammatory disease, endometriosis, polycystic ovarian syndrome, premature ovarian failure, uterine fibroids and environmental factors. Other causes of infertility in females include ovulation problems, tubal blockage, age-related factors, uterine problems, previous tubal ligation and hormone imbalance while the main cause of male infertility is poor semen quality.

Environmental factors and infertility

The etiological importance of environmental factors in infertility has been stressed [26].Toxins such as glues, volatile organic solvents or silicones, physical agents, chemical dusts, and pesticides are implicated in infertility [35]. Other potentially harmful occupational environmental exposures such as chlorinated hydrocarbons and fumicides have also been discovered to be associated with the increased link of spontaneous miscarriage in women [26]. Hence individuals having direct contact with or exposure to such chemicals have high chances of having primary or secondary infertility as the case may be. Estrogen-like hormone-disrupting chemicals such as phthalates are of particular concern for effects on babies of women.

Weight changes and infertility

Ovarian dysfunction could be caused by weight loss and excessive weight gain with body mass index (BMI) greater than 27 $^{kg}/_{m}2$ [27]. Excess weight has also been found to have effect on treatment efficacy and outcomes of assisted reproductive technique [19]. Estrogen is produced by the fat cells and primary sex organs [40] and thus, state of high body fat or obesity causes increase in estrogen production which the body interprets as birth control, limiting the chances of getting pregnant [5]. Also, too little body fat causes insufficient estrogen production and thus menstrual irregularities with anovulatory cycle [5]. Proper nutrition in early life had been linked to be a major factor for later fertility [52].

Age and Infertility

Fertility declines with age. Female fertility is at its peak between the ages of 18 and 24 years [3], while, it begins to decline after age 27 and drops at a somewhat greater rate after age 35 [25]. In terms of ovarian reserve, a typical woman has 12% of her reserve at age 30 and has only 3% at age 40 [56]. 81% of variation in ovarian reserve is due to age alone [56], making age the most important factor in female infertility. Ovulatory dysfunction is more common in younger than old couples [37].

Life style and infertility

Fertility of an individual may be influenced by life style choice [24]. Tobacco smoking and alcohol intake contribute to infertility. Cigarette smoking interferes with folliculogenesis (nicotine and other harmful chemicals in cigarettes interfere with estrogen synthesis), embryo transport, endometrial receptivity, endometrial angiogenesis, uterine blood flow and the uterine myometrium [14]. Some damage is irreversible, but stopping smoking can prevent further damage [5]. Smokers are 60% more likely to be infertile than non-smokers. Smoking reduces the chances of IVF producing a live birth by 34% and increases the risk of an IVF pregnancy miscarrying by 30% [47]. Canabis smoking, such as marijuana causes disturbances in the endocannabinoid system, potentially causing infertility [29]. Alcohol intake, on the other hand, is associated with elevated oestrogen level [39] and this elevated oestrogen level reduces FSH secretions which then suppresses folliculogenesis and results in anovulation [34].

Hormonal Imbalance and Infertility

The hypothalamus, through the release of gonadotrophin releasing hormones, controls the pituitary gland which directly or indirectly controls most other hormonal glands in the human body. Thus, alterations in the chemical signals from the hypothalamus can affect the pituitary gland, ovaries, thyroid, mammary gland and hence, hormonal abnormalities. Hormonal anomalies that affect ovulation include hyperthyroidism, hypothyroidism, polycyctic ovary syndrome (also known as Stein-Leventhal syndrome) and hyperprolactinemia [31]. Hormonal imbalance is an important cause of anovulation. Women with hormonal imbalance will not produce enough follicles to ensure the development of an ovule. Changes in hormonal balance of the hypothalamo-pituitary-adrenal axis (HPA-axis) could be caused by stress [21].

Hyperprolactinemia and infertility

Hyperprolactinemia (HP) is the presence of abnormally-high prolactin levels in the blood. Values lesser than 580 mIU/L are considered normal for women. Prolactin is produced by the anterior pituitary gland and is primarily associated with breast development during pregnancy and induces lactation. However, prolactin also binds to specific receptors in the gonads, lymphoid cells, and liver [33]. Hyperprolactinaemia may occur primarily as a result of normal physiological changes during pregnancy, breastfeeding, mental stress, hypothyroidism, or sleep. Pathologically, it may be due to diseases affecting the hypothalamus and pituitary gland or secondary to disease of other organs such as the liver, kidneys, ovaries and thyroid. Also, it may be as a result of disruption of the normal body regulations of prolactin levels by drugs, medicinal herbs and heavy metals; [33]. Hyperprolactinemia causes infertility by increasing the release of dopamine from the hypothalamus which inhibit gonadotrophin- releasing hormone (GnRH) and thus gonadal steroidogenesis and eventual infertility.

Ovarian functional problem and infertility

Infertility resulting from ovarian dysfunction may be due to absence of eggs in the ovaries or due to a complete blockage of the ovaries. Ovarian dystrophy (physical damage to the ovaries, or ovaries with multiple cysts) and luteinized unruptured follicle syndrome (LUFS), in which case the egg may have matured properly but the follicle failed to burst or even burst without releasing the egg may occur and cause anovulatory cycle [7]. Polycystic ovaries syndrome (PCOS) is usually a hereditary problem and accounts for up to 90% of cases of anovulation [8]. In PCOS the ovaries produce high amounts of androgens, particularly testosterone and thus amenorrhea or oligomenorrhea is quite common.

The increased androgen production in PCO results in high levels of luteinizing hormone (LH) and low levels of follicle-stimulating hormone (FSH), so that follicles are prevented from producing a mature egg. The hyperandrogenism can cause obesity, facial hair, and acne, although not all women with PCOS have such symptoms. PCOS also poses a high risk for insulin resistance, which is associated with type 2 diabetes.

Tubal factors and infertility

Tubal (ectopic) and peritoneal factors of importance in infertility include endometriosis [54], pelvic adhesions, pelvic inflammatory diseases usually due to Chlamidia [23], tubal occlusion [20] and tubal dysfunction. Tubal factors have similar prevalence as peritoneal factors [37]. Endometriosis is a noncancerous condition and may cause adhesions between the uterus, ovaries, and fallopian tubes, thereby preventing the transfer of the egg to the tube and thus infertility.

Uterine factors and infertility

Notable amongst uterine factors are uterine malformation such as abnormal uterine shape and intrauterine septum [46]; polyps, leiomyoma, and Asherman's syndrome [32]. Benign fibroid in the uterus are extremely common in women in their 30s. Large fibroids may cause infertility by impairing the uterine lining, blocking the fallopian tube, distorting the shape of the uterine cavity or altering the position of the cervix.

Thyroid disease and infertility

Thyroid disease had been shown to be associated with increase risk of prematurity or stillbirth [6].The prevalence of hypothyroidism in women of reproductive age (20-40 years) varies between 2% to 4% [9]. In primary hypothyroidism the serum thyroxine (T4) level is low and there is decreased negative feedback on the hypothalamo-pituitary axis. The resulting increased secretion of thyrotropin releasing hormone (TRH) stimulates the thyrotrophs and lactotrophs, thereby increasing the levels of both thyroid stimulating hormone (TSH) and prolactin [51] and thus

ovulatory dysfunction due to hyperprolactinemia. Prolactin production can also be stimulated by vasoactive intestinal peptide (VIP), epidermal growth factor and dopamine receptor agonists.

Hyperthyroidism on the other hand is characterized by suppressed serum TSH and increased thyroxine (T4), triiodothyronine (T3), or both. Hyperthyroidism in women of reproductive age is caused by Graves' disease, toxic goiter and thyroiditis. In the work of Krassas et al a higher incidence of hyperthyroidism was associated with irregular menstrual cycle ranging from hypomenorrhea, polymenorrhea, and oligomenorrhea, to hypermenorrhea [30].

Sexually transmitted disease (STD) and infertility

STDs are diseases transmitted from either sex through sexual activity with an infected partner caused by viruses, bacteria, or parasitic microorganisms. STDs are a leading cause of infertility. They are often asymptomatic but may display few symptoms, with the risk of failing to seek proper treatment in time to prevent decreased fertility [5]. Some of the identified STDs (such as syphilis, trichomoniasis, chancroid, Chlamydia, gonorrhea, herpes simplex virus, human papilloma virus, HIV, lymphogranuloma venerum) are treatable while many are not, with HIV virus being the most serious sexually transmitted infection as it eventually leads to death. STDs can also be transmitted vertically from mothers to children during pregnancy and childbirth.

Pelvic inflammatory disease (PID) and infertility

Pelvic inflammatory disease (PID) comprises of a variety of infections affecting the pelvic organs caused by different microorganisms such as bacteria and inflammatory conditions of parts of the gastrointestinal tract that lies in the pelvic area such as salpingitis from septic abortion or ascending infection. PID may be caused by sexually transmitted diseases from Chlamydia trachomatis and Gonorrhea and can eventually result into abscess formation, adhesions, scarring, tubal blockade, tubal damage, ectopic pregnancy and thus infertility. Mumps had also been reported to cause spontaneous abortion in about 27% of cases during the first trimester of pregnancy [50].

Structural obstruction and infertility

Congenital abnormalities that affect the genital tract may cause infertility. In Mullerian agenesis the vagina or the uterus fail to develop and thus infertility. Also, following pelvic surgery, postsurgical or postinfective uterine or abdominal adhesions and scarrings may occasionally result and this could restrict the movement of ovaries and fallopian tubes and cause infertility. Asherman syndrome as a result of repeated injuries to the uterine linings from multiple dilatation and curettage of the uterus can cause obstructions and secondary amenorrhea.

Chemotherapy and infertility

Studies have shown that the antral follicle count decreases after the third series of chemotherapy, whereas follicle stimulating hormone (FSH) reaches menopausal levels after the fourth series; inhibin B and anti Mullerian hormone levels also decreases following chemotherapy [49]. Drugs with high risk of infertility include procarbazine, cyclophosphamide, ifosfamide, busulfan, melphalan, chlorambucil and chlormethine ; drugs like doxorubicin, cisplatin and carboplatin have medium risk while therapies with plant derivatives (such as vincristine and vinblastine), antibiotics (such as bleomycin and dactinomycin) and antimetabolites (such as methotrexate, mercaptopurine and 5-fluoruracil) have low risk of gonadotoxicity [10].

Diagnosis of infertility

In any infertility work-up both male and female partners are considered to be a major contributor and are so investigated especially if the woman is above 35 years of age or if either partner has known risk factors for infertility. Male factors have to be removed before subjecting the female partner to any expensive but invasive test.

Medical History and Physical Examination

The first step in any infertility work up is a complete medical history and physical examination of both couple. Generally, diagnosis of hyperprolactinemia is discovered from the history of oligomenorrhea, amenorrhea, or galactorrhea. Lifestyle issues such as ciggarrete smoking, canabis, drug and alcohol abuse, and caffeine consumption may reveal the possible cause or causes of the infertility. Menstrual history and any medications being taken, and a profile of the patient's general medical and emotional health can help in deciding on appropriate tests. Also fasting measurements of plasma prolactin may be obtained to rule out hyperprolactinemia.

Diagnostic and Imaging Tests

1. Imaging tests for examining the uterus and fallopian tubes include ultrasound (particularly saline-infusion sonohysterography), hysterosalpingography, hysteroscopy, fertiliscopy, and laparoscopy. An endometrial biopsy to verify ovulation and Pap smear test are done to view pelvic organs and check for signs of infection. Magnetic resonance imaging (MRI) is the imaging study of choice as it can detect adenomas that are as small as 3-5 mm. Combinations of these imaging procedures may be used to confirm diagnoses.
2. Measuring blood urea nitrogen and creatinine is important for detecting chronic renal failure as a cause.
3. Pregnancy testing is required unless the patient is postmenopausal or has had a hysterectomy done.
4. Insulin-like growth factor-1 (IGF-1) level measurement is done in acromegaly.
5. Hormonal assay involves determining the plasma levels of hormones notably luteinizing hormone (LH) to determine ovulation in women and discover pituitary gland disorder, follicle-stimulating hormone (FSH) to determine ovarian reserve, prolactin level to confirm anovulatory cycle, and thyroid-stimulating hormone (TSH) to check for thyroid gland problems [55]. A thyroid stimulating hormone (TSH) level of between 1 and 2 is considered optimal for conception. Measurements of progesterone in the second half of the cycle help to confirm ovulation.
6. Immunological tests are done to determine antisperm antibodies in the blood and vaginal fluids. Antibody infertility blood tests are conducted to detect antibodies that destroy the spermatozoa.
7. A postcoital test, may be done soon after intercourse to check for problems with sperm surviving in cervical mucous.

Prevention of infertility

Some cases of infertility may be prevented through identified interventions:

- Maintaining a healthy lifestyle: Excessive exercise, consumption of caffeine and alcohol, and smoking (tobacco and marijuana) are all associated with decreased fertility, hence should be avoided. Eating a balanced and nutritious diet, fruits and vegetables (plenty of folates), and maintenance of normal body weight are associated with better fertility prospects.
- Preventing or treating existing diseases: Identifying and controlling chronic diseases such as diabetes, hyperthyroidism and hypothyroidism increases fertility prospects. Regular physical examinations (including Pap smears) help to detect early signs of infections or abnormalities.
- Sexually transmitted diseases can be prevented by abstinence from sex or the practice of “safer sex” strategies for people having multiple sex partners, including mutual monogamy, non-penetrative sex, and the correct and consistent use of barrier contraceptive methods, particularly latex male condoms and polyurethane vaginal sheath (female condom).
- Prompt treatment of STDs.
- Not delaying parenthood: Fertility starts to decline after age 27 and drops at a somewhat greater rate after age 35 [25]. Women whose biological mothers had unusual or abnormal issues related to achieving pregnancy may be at particular risk of premature menopause that can be mitigated by not delaying parenthood.

Treatment

Preconception medical care and counseling is advisable for all those planning a pregnancy failure of which the couple may choose to remain childless or consider adoption, or non-spousal sperm options.

Treatment modalities for infertility include:

1. Weight reducing drugs: In obese anovulatory infertile women, a loss of 5-10 % of body weight had been discovered to be enough to restore reproductive functions in 55- 100% of women within 6 months [11].
2. Induction of ovulation using gonadatrophins, Human Menopausal Gonadotrophin (HMG)
3. Bromocriptine in hyperprolactinemic females.
4. Clomifene citrate-human menopausal gonadotrophin (CC-HMG) combination. [48].
5. Hormone therapy (e.g., Perganol).
6. Surgical intervention.
7. Artificial Insemination (AI): AI may be achieved by intracervical or intrauterine insemination. It is performed in an ovulating woman with patent tubes.
8. In Vitro Fertilization (IVF): IVF could be used to treat women with damaged fallopian tubes and endometriosis or in cases of unexplained infertility. A standard IVF requires the presence of a functioning fallopian tube and the procedures include gamete intrafallopian transfer (GIFT), zygote intrafallopian transfer (ZIFT) or GIFT-ET which is a combination of GIFT and IVF.

9. Intracytoplasmic Sperm Injection (ICSI): ICSI is used when male infertility is the main problem. It involves injecting a single sperm into an egg obtained from in vitro fertilization (IVF).

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