



Daffodil
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Project on
A Review of Female Infertility; Important Etiological Factors and Management

[In the partial fulfillment of the requirements for the degree of Bachelor of Pharmacy]

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Faculty of Allied Health Sciences,
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APPROVAL

This project paper, “**A review of Female Infertility; important etiological factors and management.**”, submitted to the Department of Pharmacy, Faculty of Allied Health Sciences, Daffodil International University, has been accepted as satisfactory for the partial fulfillment of the requirements for the degree of Bachelor of Pharmacy and approved as to its style and contents.

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DECLARATION

I hereby declare that this project report, “**A review of Female Infertility; important etiological factors and management.**”, is done by me under the supervision Ms. Aklima Akter Assistant Professor, I am declaring that this Project is my original work. I also declare that neither this project nor any part thereof has been submitted elsewhere for the award of Bachelor or any degree.

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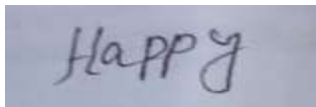
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Finally, I would like to express my gratitude towards my parents and other family members for their kind cooperation and encouragement which helped me in completion of this project.



My Parents

The persons who always encourage me in every sphere of my life

Abstract

Subfertility or infertility is a significant societal and psychological burden on couples, particularly on African women. According to estimates, female factors and unexplained infertility typically account for 50–80% of cases of infertility in Nigeria, necessitating a review of the different research studies. The various causative variables that contribute to female infertility were examined in this assessment, and an effort was made to update the knowledge already on hand regarding its treatment. The primary goal of this review is to produce data that could be used as guidelines in assessing female infertility. According to the literature reviewed on female infertility, some of the suggested good preventive measures to deal with infertility between many infertile women include a loss of 5–10% of body weight in obese an ovulatory infertile woman, keeping up an active lifestyle, preventative measures and prompt treatment of sexually transmitted diseases, and not delaying parenthood. Letrozole and anastrozole are examples of aromatase inhibitors that block estradiol biosynthesis, lessen estradiol impact on the hypothalamus-pituitary, and raise the production of FSH in PCOS-afflicted women. Clomiphene intolerant women with PCOS are those who have tried normal clomiphene doses but still have not been able to ovulate. To lowering insulin levels is a treatment objective for PCOS-affected women. An oral biguanide antihyperglycemic medication called metformin has been authorized for the management of type 2 diabetes mellitus.

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Chapter 1

Introduction

1. Introduction

Infertility is the inability of a pair to become pregnant over the period of an estimate of one year (in a woman underneath the age of 35) or six months (in a woman over the age of 35), even when they have regular, uncontrolled sexual contact at a frequency of three to four times per week. [1] The incapacity to carry a pregnancy to term and birth a live child is another name for infertility. The main or secondary cause of infertility may be the woman, the man, or both. Couples with primary infertility have never been able to procreate, whereas those with secondary infertility have trouble getting pregnant after giving birth (either carried the pregnancy to term or had a miscarriage). [2] If a partner has changed within the past year, secondary infertility is not present, which has its own peculiar opportunities of being infertile. Cervical factors include cervical stenosis, antisperm antibodies, insufficient, aggressive, or non-receptive cervical mucus, and infections from sexually transmitted diseases like Chlamydia, gonorrhea, trichomonas, mycoplasma hominis, and ureaplasma urealyticum that prevent spermatozoa from reaching the uterus. [3] The likelihood of sterility between several women rises with age. In one research, 12% and 21% of women reported infertility at ages 32 and 38, correspondingly. Since the female partner's fertility prospective declines after age 35, the majority of experts advise starting an infertility evaluation six months after trying to conceive in women between the ages of 35 and 40 and three months in women over 40. Women with established infertility reasons, such as amenorrhea, should initiate an evaluation right away to determine the cause and formulate a therapy strategy. [4]

1.1 Epidemiology of female infertility

The likelihood of sterility between several women rises with age. In one research, 12% and 21% of women reported infertility at ages 32 and 38, correspondingly. Since the female partner's fertility prospective declines after age 35, the majority of experts advise starting an infertility assessment six months after trying to conceive in women between the ages of 35 and 40 and three months in women over 40. [5] Women with established infertility reasons, such as amenorrhea, should initiate an evaluation right away to determine the cause and formulate a therapy strategy.

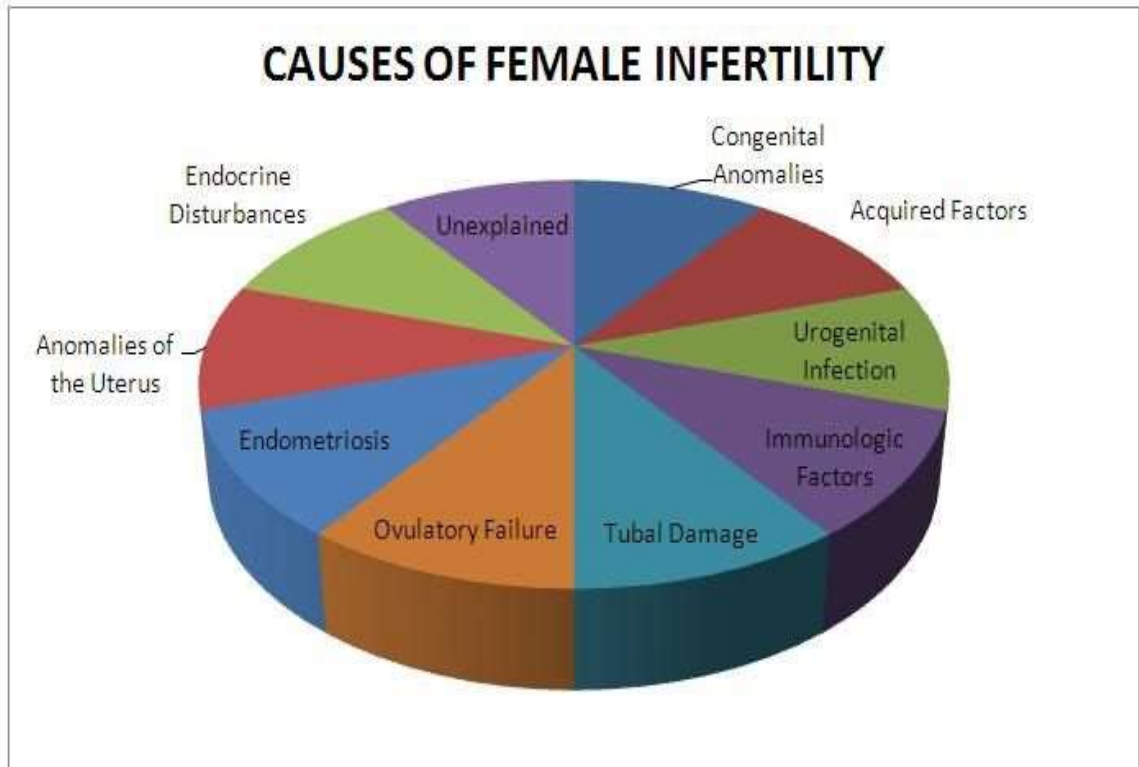


Figure 1: Epidemiology of female infertility [6]

Infertility may have a variety of reasons. It can be challenging to determine the precise cause, and some partners experience "inexplicable" or "multifactorial" infertility (multiple causes, often both male and female factors). [7] The following are some potential reasons of female factor infertility: Polyps, fibroids, a septum, or adhesions within the uterine chamber are examples of uterine issues. Other anomalies (like a septum) are present at birth, so although polyps and fibroids can develop on their own at any moment. After a procedure like such a dilation and curettage, adhesions may develop (D&C). [8]

The reproductive tubes are having issues:

Infertility due to the "tubal factor" is most frequently caused by pelvic inflammatory disease, which is typically brought on by chlamydia and gonorrhea. [9]

Ovulation issues:

A woman may not ovulate (release an egg) on a regular basis for a variety of causes. Ovulation can be impacted by a variety of factors, including hormonal imbalances,

pituitary tumors, past eating disorders, substance misuse, thyroid issues, and extreme stress. [10]

Difficulties with egg quality and quantity:

All of a woman's eggs are present when she is born, but this quantity may "run out" prior to actually menopause. Additionally, some eggs will have an incorrect amount of chromosomes, which prevents them from fertilizing or developing into healthy fetuses. All of the embryos may be impacted by certain chromosomal problems (like "balanced translocation"). Others are arbitrary but increase in frequency as a lady ages. [11]

1.2 Risk factor of female infertility

An underlying health problem that affects the fallopian tubes, conflicts with ovulation, or results in hormonal issues may be the root of infertility. Such medicinal disorders involve uterine fibroids, polycystic ovarian syndrome, endometriosis, pelvic inflammatory disease, premature ovarian failure, and environmental factors. [12] Poor semen quality is the main consequence of male infertility, while other causes of infertility in females involve ovulation issues, tubal obstruction, age-related variables, uterine issues, prior tubal ligation, and hormone imbalance. [13]

The environment and sterility

Environmental variables play a significant role in the etiology of infertility, which has been emphasized. Infertility is linked to toxins like adhesive, silicones, volatile organic solvents, physical agents, chemical dusts, and pesticides. [14] It has also been found that exposure to other possibly hazardous occupational environmental factors, such as fumicides and chlorinated hydrocarbons, is linked to a higher risk of unplanned miscarriage in women. [15] As a result, people who come into touch with or are exposed to such chemicals have a high risk of developing primary or secondary infertility, depending on the situation. Chemicals that alter hormones similar to estrogen, the same as phthalates, pose a special risk to the health of female babies. [16]

Alterations in weight and sterility

Weight loss and extreme weight increase with a body mass index (BMI) of more than 27 kg/m² may contribute to ovarian malfunction. Additionally, it has been discovered that excess weight affects the effectiveness of therapy and the results of assisted reproductive technology. [17] Because fat cells and the main sex organs create estrogen, a high body fat or obese state increases estrogen production, which the body perceives as birth control and lowers the likelihood of becoming pregnant. Additionally, too few body fat results in insufficient estrogen production, which leads to irregular menstruation and an ovulatory period. Early nutrition had been found to play a significant role in subsequent fertility. [18]

Infertility and Maturity

Age causes a decrease in fertility. Female fertility reaches its peak between the ages of 18 and 24. Thereafter, it starts to diminish, and after age 35, it starts to decline somewhat more quickly. [19] Typically, a woman's ovarian reserve is between at age 30, a woman has 12% of her resource, and at age 40, she only has 3%. Age is the most significant contributing factor to female infertility because it accounts for 81% of the variance in ovarian reserve. In young couples compared to older couples, ovarian malfunction is more prevalent. [20]

Infertility and way of life

An individual's lifestyle choices may have an impact on their fertility [24]. Alcohol consumption and tobacco use both affect fecundity. The folliculogenesis process is hampered by smoking because nicotine and other harmful compounds in cigarettes prevent the synthesis of estrogen. [21] Smoking also affects embryo movement, endometrial responsiveness, endometrial angiogenesis, uterine blood supply, and the uterus myometrium. Although some damage is irreversible, quitting smoking can halt further harm. Infertility is 60% more common in users than non-smokers. Smoking increases the possibility that an IVF pregnancy will miscarry by 30% and decreases the likelihood that an IVF pregnancy will result in a live birth by 34%. The endocannabinoid pathway is disturbed by smoking, including marijuana, which may result in sterility. [22]

Hormonal Imbalance and Infertility

By producing gonadotrophin-releasing hormones, the hypothalamus regulates the pituitary gland, which in turn regulates almost all other hormonal glands in the body either immediately or tangentially. The pituitary gland, ovaries, thyroid, and mammary duct can all be impacted by changes in the chemical cues coming from the hypothalamus, which can lead to hormonal disorders. [23] Hyperthyroidism, hypothyroidism, polycystic ovary disease (also called Stein-Leventhal syndrome), and hyperprolactinemia are among the hormonal abnormalities that interfere with conception. Anovulation has a number of hormonal causes, particularly disequilibrium. Women with hormonal imbalances won't make sufficient follicles to guarantee the ovule's growth. Stress may alter the hypothalamo-pituitary-adrenal axis's (HPA- axis's) hormonal equilibrium. [24]

Hyperprolactinemia and infertility

The existence of abnormally elevated prolactin levels in the blood is known as hyperprolactinemia (HP). For women, values below 580 mIU/L are regarded as typical. The anterior pituitary gland produces prolactin, which is mainly linked to breast growth all through pregnancy and stimulates lactation. [25] Prolactin does, moreover, also attach to particular receptors in the liver, lymphoid cells, and gonads. Physiological alterations that are common during pregnancy, breastfeeding, stress, hypothyroidism, or sleep may lead to hyperprolactinaemia. [26] Pathologically, it might result from conditions affecting the brain and pituitary gland, or it might be a complication of conditions affecting other organs like the thyroid, liver, kidneys, ovaries, or kidneys. Additionally, medications may be to blame for interfering with the body's natural mechanisms for controlling prolactin levels. [27]

Ovarian functional problem and infertility

Ovarian insufficiency may cause infertility if there are no embryos in the ovaries or if the ovaries are completely blocked. Both luteinized unruptured follicle syndrome (LUFS), in which the egg may have grown appropriately but the follicle missed to burst or perhaps even burst without having to release the egg, and ovarian dystrophy (physical damage to the ovaries or ovaries with multiple cysts) may occur and result in an anovulatory cycle.

[28] Up to 90% of instances of anovulation are caused by the hereditary condition polycystic ovaries syndrome (PCOS), which is typical. Amenorrhea or oligomenorrhea is quite prevalent in PCOS due to the high levels of androgens, especially testosterone, that are produced by the ovaries. [29]

1.3 Initial Infertility Evaluation

Early on in the infertility assessment, three procedures should be finished: a tubal catheterization test, ovulation documentary evidence, and semen analysis. A comprehensive history and physical examination, a semen investigation, recording of proficient ovulation, confirmation of the health of the female reproductive system and the tubes, and a measurement of the uterine cavity are all standard parts of the infertility review. [30] Male infertility assessment of the semen analysis. As will be covered in more detail later, ovulation can be presumed to have occurred if there has been a background of regular menstruation every 28 days, or it can be confirmed by a serum progesterone level higher than 3 ng/mL or the histological evidence of secretory changes on an endometrial biopsy. [31] Early in the infertility assessment, a hysterosalpingogram (HSG), a hysterosalpingo-contrast ultrasound (HyCoSy), or a laparoscopy should be used to record tubal stability. An HSG, HyCoSy, or hysteroscopy can all be used to find uterine anomalies. For the identification of proximal tubal occlusion, an HSG is linked with a false-positive rate of about 15% despite having good sensitivity and few false positives for the identification of distal tubal illness. [32] This implies that if the HSG shows intermediate tubal obstruction, a second test (such as specific interventional radiology catheterization of each tube, hysteroscopic cannulation, or laparoscopy with tubal lavage) should verify the observation. The HSG can also detect significant intrauterine abnormalities and show how the uterine cavity is shaped. [33]

1.4 Infertility and Cancer Risk

Although it is unclear whether fertility treatment on its own raises the chance of breast, endometrial, and ovarian cancers, infertility is a potential risk for these diseases. The infertile community is characterized by traits like null parity, late age at first birth, delayed age at menopause, and anovulation, which are also linked to a higher chance of ovarian, endometrial, or breast cancer. [34] A 2017 Cochrane review of four studies and 19 614

participants found that sub fertile women treated with clomiphene citrate had a higher risk of endometrial cancer than controls (risk ratio, 1.87 [95% CI, 1.00-3.48]), but it was unable to determine whether this affiliation was due to PCOS or publicity to clomiphene itself. [35] A 2019 Cochrane review that examined the uncertainties of ovarian cancer in women taking ovarian-stimulating medications for infertility (37 experiments, 4 684 724 women) came to the conclusion that the evidence was inconclusive and the existing studies had poor methodological quality, short follow-up periods, and did not account for confounders. [36] Numerous published studies and meta-analyses covering ovulation inducement and IVF, as well as 2 with more than 30 years of obey, found no evidence linking hormonal infertility treatments to an increased chance of breast cancer. A 2019 Cochrane review that examined the uncertainties of ovarian cancer in women taking ovarian-stimulating medications for infertility (37 experiments, 4 684 724 women) came to the conclusion that the scientific proof was inconclusive and the existing studies had poor methodological quality, short follow-up periods, and did not account for confounders. [37] Numerous published studies and meta-analyses covering ovulation inducement and IVF, as well as 2 with more than 30 years of obey, found no evidence linking hormonal infertility treatments to an increased chance of breast cancer. Infertile women may therefore have a higher risk of developing invasive ovarian, endometrial, and breast cancer, but there is no concrete proof that taking reproductive drugs increases this risk. [38] 88 Male infertility is linked to an increased chance of cancer overall, just like infertility in women. In the years following an infertility assessment, there was an elevated incidence of all cancers (600 cases reported, 333.41 instances predicted; hazard ratio, 1.80 [95% CI, 1.66-1.95]), according to an examination of US data available from 76 083 infertile males. [39]

Chapter 2

Purpose of the study

2.1 Purpose of the study

Infertility is the inability to conceive after at least a year of attempting (or 6 months if the woman is over age 35). Infertility is also referred to as a cycle of losses. Age, physical issues, hormone issues, and behavioral or environmental variables can all contribute to female infertility. The aim of this review of following points:

- The main aim of this review is to generate information which could act as guideline in the evaluation of female infertility.
- This activity reviews the evaluation, management, and treatment of female infertility.
- To know developing guidelines on the prevention, diagnosis of woman infertility.
- To know the risk factor of this illness.
- To know the epidemiology of female infertility.

Chapter 3

Methodology

3.1 Methodology

- I have been started work for this in January 2023.
- I have been tried my best to collect all data by using Key phrases including "**female infertility**" "**female infertility etiology**" "**female infertility treatment,**" and "**female infertility diagnostic.**" were searched for utilizing web-based search engines, academic bibliographic databases, PubMed, Research Gate, Google scholar and Medline.
- The examination is led by a literature review, around 40 papers are reviewed for this assessments.
- Trying to gathered all data between 1995-2022 and all the work done in MS Word to make the process easy.
- I was learned more by reading every composed review paper. The information acquired has been finally summarized.

3.2 Data analysis strategy

Data assembly, cleansing, and organization are mutual actions encompassed in data analysis techniques. The data must go through these events, which typically involve using data investigation software, in order to be prepared for business use. Data analytics, another name for data analysis, is well-defined as the science of inspecting raw data in order to make defensible extrapolations about the data.

Chapter 4

Literature Review

4.1 Diagnosis and Management of Female Infertility

One of the most common chronic health conditions affecting young adults is infertility, which is described as a year of unsuccessful attempts at conception. Infertility, which affects at least 6 million US partners, is clinically different from recurrent spontaneous pregnancy loss. In vitro conception has changed how female infertility is treated (IVF). A similar transformation has occurred in the treatment of male infertility thanks to intracytoplasmic sperm injection (ICSI), which was first described as an IVF laboratory procedure in 1992. The processes of fertilization and implantation have been better understood thanks to in vitro fertilization and ICSI, which has improved understanding of potential abnormalities in fertility both before and after fertilization as well as prospective flaws in embryonic development. But due to the expense and intricacy of the procedure, IVF and ICSI are still not widely used. [40]

4.2 Anatomical causes of female infertility and their management

Endometriosis, congenital/acquired uterine discrepancies, and post-infectious tubal injury are the three main anatomical factors that affect fertility in women. Infertility, pregnancy loss, and other obstetric complications can result from inherited (septate uterus) and obtained (myomas and synechiae) uterine illnesses. The most frequent reason for tubal injury is pelvic inflammatory disease. With reproductive outcomes that favorably compare with those of in vitro fertilization, surgery is still a viable treatment choice for tubal factor infertility. Women of reproductive age are frequently affected by the gynecologic disease endometriosis, which can lead to pain and infertility. Endometriosis-related infertility has an enigmatic cause, which points to a multifactorial process combining immunologic, genetic, and environmental variables. Endometriosis is extremely common, but the precise mechanisms underlying its pathogenesis are still uncertain. Women with endometriosis may benefit from particular regimens of medical, surgical, and psychological therapies that improve their quality of life. The bulk of the time, surgical endometriosis management has led to marked increases in fertilization rates. Future treatments for endometriosis may be founded on immunologic principles due to the clear connections between the condition and the immune response. [41]

4.3 Environment, Lifestyle, and Female Infertility

Our everyday habits and other lifestyle factors play a big part in determining how healthy we are as a whole. These lifestyle decisions are primarily driven by individual tastes and our immediate social context. We constantly interact with our surroundings, which affects physiology, in response to lifestyle factors. Women's fertility has been linked to a number of factors, but lifestyle-related variables have drawn a lot of focus recently. The reproductive age for women has steadily risen to the 30s as a result of social and professional pressure. Modern lifestyle and postponed childbearing present a larger window of opportunity for various behavioral and genetic perturbations to infiltrate and impact fertility. Experimental research on animal models have looked into the mechanism of action of lifestyle, environment, and female reproductive health, which has been supported by clinical studies. The neuroendocrine processes are typically the targets of these variables, which causes metabolic disturbances. This review seeks to analyze the possible connections between various neuroendocrine routes and lifestyle and environmental factors, and it also discusses how these connections may eventually have an adverse effect on female physiology and impair reproductive ability. [42]

Chapter 5

Result & Discussion

5.1 Management of female infertility

Management of female infertility	Mechanism of action	Reference
Letrozole	Letrozole and anastrozole are examples of aromatase inhibitors that block estradiol biosynthesis, lessen estradiol impact on the hypothalamus-pituitary, and raise the production of FSH in PCOS-afflicted women. It has been proven that letrozole at doses of 2.5 to 7.5 mg daily for 5 days and anastrozole at a dose of 1 mg daily for 5 days can trigger menstruation in PCOS-afflicted women.	43-44
Clomiphene	The nonsteroidal estrogen agonist-antagonist clomiphene, which is linked to tamoxifen and diethylstilbestrol, was first created in 1956. Clomiphene was given FDA approval in 1967 after Greenblatt et al. found it to be effective in the stimulation of ovulation in 1961. (see also Chapter 30). Enclomiphene (E, trans) and zuclomiphene (Z, cis) are combined in a racemic combination to create CC, with a ratio of roughly 3 to 2. The Z-isomer might be more effective at causing menstruation than the trans isomer.	45-46
Clomiphene Plus Glucocorticoid Induction of Ovulation	Clomiphene intolerant women with PCOS are those who have tried normal clomiphene doses but still have not been able to ovulate. A most suitable next steps in therapy for PCOS-positive, clomiphene-resistant women are gonadotropin injections or laparoscopic ovarian extraction, according to a consensus group of fertility experts. Moreover, many women may find these choices to be unaffordable. What therapy can be recommended for the PCOS patient who is clomiphene-resistant? If clomiphene and dexamethasone are used in conjunction to help clomiphene-resistant women, several of them will ovulate.	47-49
Clomiphene and Nonclassical Adrenal Hyperplasia	Numerous experts advise giving glucocorticoids, including such prednisone 5 to 7.5 mg daily, to infertile anovulatory women with nonclassical adrenal hyperplasia (NCAH) brought on by alterations in 21-hydroxylase in order to induce ovulation. On ultrasonography, some women with lengthy NCAH do, moreover, show signs of polycystic ovarian morphology and ovarian hyperandrogenism. Infertile women with NCAH can use clomiphene alone or clomiphene plus glucocorticoids to trigger ovulation and obtain pregnancy.	50-51
Clomiphene and Estrogen-Progestin Contraceptive Pretreatment	An initial outstanding features of circulating testosterone is a health risk for failure to ovulate with clomiphene. By reducing serum testosterone before starting a clomiphene cycle, estrogen progestin pretreatment may increase the likelihood of ovulation. In one small case reports and one called the process,	52-53

	it was discovered that taking an estrogen-progestin contraceptive pill continuously for two months before starting clomiphene therapies reduced circulating testosterone and increased the likelihood of ovulation and pregnancy in PCOS patients who had been taking the drug 150 mg per day for five days without success.	
Clomiphene Plus Gonadotropin Induction of Ovulation	Injections of gonadotropins can be added to clomiphene therapy in order to trigger ovulation in women who do not ovulate when taking standard doses of CC. 103 This method of ovulation induction has the primary advantage of reducing the amount of gonadotropins required to induce ovulation during each cycle. The early boost in LH and FSH brought on by clomiphene makes the follicles more responsive to gonadotropin injections.	54
Clomiphene and Metformin	A prevalent endocrine abnormality seen in women with PCOS is hyperinsulinemia. By inhibiting the production of hepatic sex hormone-binding globulin and potentially by acting as a co-gonadotropin with LH to stimulate thecal cell androgen biosynthesis, the increased insulin levels add to reproductive malfunction. Thus, lowering insulin levels is a treatment objective for PCOS-affected women. An oral biguanide antihyperglycemic medication called metformin has been authorized for the management of type 2 diabetes mellitus.	55-56

Table 1: Management of female infertility

5.2 Diagnosing Female Infertility

Blood tests: A variety of blood tests are useful in identifying a number of possible causes of infertility, including abnormal hormonal levels, the existence of cystic ovaries, cervical issues, etc. [57]

Laparoscopy: This process includes making a small opening close to the belly button and introducing a fiber-optic camera and thin tube to view the uterus, ovaries, and fallopian tube's outer lining. Particularly in instances of endometriosis, which is brought on by the development of endometriotic tissues in other areas of the body, laparoscopy aids medical professionals in searching for abnormal growth in the pelvic region. [58]

Hysterosalpingography (HSG): During an HSG, a dye or saline is inserted into the cervix via X-ray or ultrasound in order to look for fallopian tube blockage. [59]

Chapter 6

Conclusion

6.1 Conclusion

Fertility issues can be avoided by leading a healthy lifestyle, visiting the doctor frequently, and keeping a normal body weight. Prospects for conception are improved by recognizing and treating persistent conditions like diabetes, hyperthyroidism, and hypothyroidism. Where infertility is a widespread and serious issue, health care programs should be implemented to address it. The need for healthcare should be related to the cultural realities of particular places. Important conditions for solving the issue include providing infertile women with medical and socioeconomic assistance. Medications, minor surgical procedures, laparoscopic methods, hormonal therapy, and preconception failure protection can all be used to address female infertility. All scientific and medical experts who work to end female infertility will benefit from the study.

Chapter 7

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