Project On

A review on Polycystic Ovary Syndrome (PCOS) Epidemiology, Symptoms, Diagnosis, Risk Factors & Treatment

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

Submitted To

The Department of Pharmacy,

Faculty of Allied Health Sciences,

Daffodil International University

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APPROVAL

This Project, **A review on Polycystic Ovary Syndrome (PC0S) Epidemiology, Symptoms, Diagnosis, Risk Factors & Treatment**, 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, at this moment, announce that I am carrying out this project study under the supervision of "Mr. Md. Mominur Rahman, Lecturer, Department of Pharmacy, Faculty of Allied Health Sciences, Daffodil International University, Impartial Compliance with the Bachelor of Pharmacy Degree Requirement (B. Pharm). This project, I declare, is my original work. I also state that neither this project nor any part thereof has been submitted for any elsewhere.

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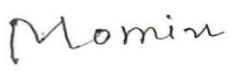

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Abstract

Several illnesses are gender specific. Gynecological problems affect the female reproductive system.While some of these female health issues can be resolved others are fatal or chronic. A few of these conditions affect fertility. Hormonal disorders are becoming more and more common as a result of the increase in chemical invasion and exposure which are largely endocrine disruptors. Amenorrhea, dysmenorrhea endometriosis, polycystic ovary syndrome, fibroids, infertility, ovarian cancer, miscarriage, ectopic pregnancy, preterm delivery etc are a few of these frequently seen reproductive and hormonal disorders. PCOS is an endocrine condition that affects females who are of reproductive age. Infertility, hypertension, anxiety, (Witchel et al., 2020) depression, insomnia, eating disorder, insulin resistance, obesity, and cardiovascular disorders are just a few of the health concerns brought on by this syndrome. A polygenic, polyfactorial, inflammatory, dysregulated steroid state, auto immunological disease, PCOS primarily manifests as a result of poor lifestyle choice (Patel, 2018). From before conception and continuing into the post-menopausal years, PCOS has an impact on women's health throughout their whole lifecycle.(Witchel et al., 2020). Treatment for excess androgen symptoms includes the use of spirolactone and finasteride, metformin, oral contraceptive pill (OCP), progesterone, folic acid (Susan M Sirmans, 13 Dec 2022). Clomiphene, laparoscopic ovarian drilling, gonadotropins, and assisted reproductive technology are among the treatments for infertility. The prevalence, kinds, symptoms, causes, genetic variables, pathophysiology, etiology, risk factors, and various treatment modalities for PCOS are all summarized in this review.

Keywords: Fertility, Amenorrhea, Endometriosis, Ovarian Cancer, Miscarriage, Ectopic pregnancy, Preeclampsia, Preterm Delivery, Depression, Anxiety.

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Chapter one
Introduction

A review on Polycystic Ovary Syndrome (PCOS) Epidemiology, Symptoms, Diagnosis, Risk Factors & Treatment

1.1 Introduction

With global prevalence up to this point ranging from 5% to 15%, the polycystic ovarian syndrome (PCOS) is acknowledged as one of the most prevalent endocrine abnormalities in women. Overall, the condition seems to be a complex genetic feature that dates back at least 50,000 years and is quite old (Ricardo Azziz M.D., julu 2016). The heterogeneous illness known as polycystic ovarian syndrome (PCOS) affects females and is connected to an endocrine reproductive disorder. Ages 18 to 44 for females are affected (Nida Ajmal, Julu, 2019). According to the proceedings of an expert conference sponsored by the National Institutes of Health (NIH) in April 1990, which noted the disorder's presence of 1) hyperandrogenism and/or hyperandrogenemia, 2) oligo anovulation, and 3) exclusion of known disorders, polycystic ovary syndrome (PCOS) is most commonly defined. A different expert conference, convened in Rotterdam in May 2003, classified PCOS by two of the three following characteristics after excluding associated disorders: oligo- or anovulation, clinical and/or biochemical indicators of hyperandrogenism, or polycystic ovaries are some examples of these conditions. The Rotterdam 2003 definition essentially broadened the NIH 1990 criteria by including two new phenotypes: 1) ovulatory women with polycystic ovaries and hyperandrogenism, and 2) oligo anovulatory women with polycystic ovaries but no hyperandrogenism (Azziz, 1 March 2006). PCOS is regarded as a complex condition with multiple genetic, metabolic, endocrine, and environmental problems even though the cause is still not fully known. According to mounting evidence, PCOS can start during pregnancy in genetically predisposed individuals, presents clinically throughout adolescence, and persists throughout a woman's reproductive years. Moreover, it may put patients at higher risk for metabolic issues like diabetes, hypertension, and cardiovascular disease, particularly after menopause. It might result in anovulatory infertility during the fertile window and be linked to a higher prevalence of prenatal problems such miscarriage, gestational diabetes, and preeclampsia. Hence, early diagnosis is essential to allow for close monitoring and to try to lower the likelihood of such problems. Insulin resistance, which most commonly affects obese or overweight women but can also occur in lean PCOS women, is now increasingly

acknowledged as a crucial factor in this complicated condition. In conjunction with luteinizing hormone (LH), it influences the formation of sex hormone-binding globulin (SHBG) by the liver and ovarian steroidogenic enzymes, which determine hyperandrogenism (V. De Leo, 2016). A strong index of suspicion is required since PCOS in adolescents is challenging to diagnose. Because insulin resistance/hyperinsulinemia, a significant component of the syndrome, increases the risk of type 2 diabetes, dyslipidemia, and cardiovascular consequences, prompt evaluation and treatment are essential. A detailed family history, ruling out alternative causes of hyperandrogenism, and the right lab tests should all be part of the diagnosis of PCOS in teens. Treatment is debatable because there aren't many controlled clinical trials. Lifestyle changes, oral contraceptives, and insulin sensitizers are examples of therapeutic possibilities. To ascertain whether these methods are helpful in altering the natural history of the reproductive and metabolic outcomes without inflicting excessive harm, long-term follow-up is required. (Julia Warren-Ulanch MD (Adult and Pediatric Endocrinology Fellow, Director, & Di, JUNE, 2006)

Figure 1 : PCOS (Source -Indira IVF)

A review on Polycystic Ovary Syndrome (PCOS) Epidemiology, Symptoms, Diagnosis, Risk Factors & Treatment

1.1.1 History Of Poly Cystic Ovary Syndrome (PCOS)

PCOS was named for the ovarian morphology and was found by Stein and Leventhal. The authors described seven women who had enlarged ovaries with numerous tiny follicles, hirsutism, and menstrual irregularities in common. The later researchers validated their suspicion that bilateral cystic ovaries were caused by improper hormonal stimulation. When choices like clomiphene and follicle-stimulating hormone (FSH) were accessible, medical treatment versus surgical ovaries-removal became the recommended course of action. When laparoscopic treatment became common, interest in the surgical management of PCOS increased. In the history of PCOS, newer technology like ultrasound to imaging ovaries were a breakthrough, and the simplicity of this approach made the diagnosis of PCOS simpler. Unfortunately, this had the unanticipated outcome that many women were diagnosed with polycystic ovaries but with moderate or no other symptoms of PCOS. This gave rise to the phrase polycystic ovarian morphology, whose relevance is still up for discussion. It has been argued that the widespread adoption of the Rotterdam criteria, which included oligo-anovulatory females with polycystic ovarian morphology without clinical or biochemical evidence of hyper androgenism, is premature and will result in unnecessary diagnosis, laboratory testing, and likely lifelong consequences for these females. The precise etiology of this illness is still unknown even after so many years since its discovery; it is currently thought to be multifactorial with a significant hereditary component. Despite the fact that insulin resistance (IR) is frequently observed in PCOS-affected females, no diagnostic criteria incorporate it.(Ganie et al., 2019)

1.1.2 Prevalence

Between 6% and 26% of people globally have PCOS (Gade, et al., May 2022). A systematic review and meta-analysis of published studies that reported PCOS prevalence according to at least one diagnostic criterion subset were undertaken by Bozdag et al. According on the parameters utilized, their findings showed that the prevalence of PCOS varies globally and

ranges from 6% to 10%. Comparable epidemiological investigations came to the conclusion that the prevalence estimates from the Rotterdam and Androgen Excess Societies were around twice as high as those obtained using the National Institutes of Health standards. There are a number of reasons why PCOS prevalence estimates can vary. Globally, the prevalence of T2D (Type 2 Diabetes) is rising, and most of its sufferers are women. T2D and PCOS are co-morbidities, and PCOS has significant metabolic, cardiovascular, and psychosocial effects. Thus, early detection and treatment of PCOS in this high-risk population are essential. Adults with PCOS and T2D are linked in both directions. Studies on adolescents have revealed that girls with PCOS had lower insulin sensitivity and compensatory hyperinsulinemia. Insulin resistance is a major factor in the etiology of PCOS. Insulin improves the pituitary gland's receptivity to hypothalamic gonadotropin-releasing hormone, which in turn stimulates luteinizing hormone synthesis. Although prior research revealed that insulin resistance brought on by obesity and hyperinsulinemia may contribute to the etiology of PCOS, insulin resistance in (Milena Cioana, et al., February 15, 2022).PCOS individuals may exist independently of BMI. Obesity appears to just marginally enhance the likelihood of PCOS and may be a PCOS referral bias. The metabolic syndrome's symptoms of hypertension, hyperglycemia, and dyslipidemia are all linked to PCOS. Moreover, cardiovascular risk factors are more common in people with PCOS. PCOS is also prone to psychiatric comorbidities such anxiety (18%), sadness (16%), and attention-deficit/hyperactivity disorder (9%). Patients with PCOS have significantly lower health-related quality of life, with issues with body weight, irregular menstruation, and a sense of not having control over one's health all playing significant roles (Milena Cioana, et al., February 15, 2022).

1.1.3 Epidemiology Of PCOS

PCOS is a condition that is challenging to define. It is a syndrome, which is a collection of recognizable patterns of symptoms or abnormalities that point to a certain medical condition. One implication is that a single result does not, by itself, allow for the formation of the diagnosis.

The definition has also changed throughout time. Originally documented as a case of a bearded woman with diabetes mellitus two centuries ago by Stein and Leventhal. further descriptions from the previous century The European Society of Human Reproduction/American Society for Reproductive Medicine (ESHRE/ASRM)-Sponsored PCOS Consensus Workshop Group in Rotterdam created a modern 21st-century description in 2003. With these restrictions in mind, it is generally agreed that the prevalence of PCOS is between 5 and 10%, while that of polycystic ovaries alone is between 2 and 23%.

According to the 2003 definition, PCOS must have two of the following three symptoms: (i) oligo- and/or anovulation, (ii) clinical and/or biochemical signs of hyperandrogenism, (iii) polycystic ovaries, and (iv) the exclusion of other etiologies, such as congenital adrenal hyperplasia, androgen-secreting tumours, or Cushing's syndrome. The most widely used definitions of the concepts stated above must be taken into account because there may be various interpretations of them.

1.1.4 Oligo and anovulation

Oligo and or anovulation commonly manifests as oligomenorrhoea (fewer than nine menses per year) or dysfunctional uterine bleeding (which is irregular or unpredictable). It is also accepted that any cycle lasting 35 days is abnormal.

1.1.5 Clinical and or Biochemical Signs of Hyperandrogenism

Hirsutism, which refers to the excessive growth of coarse, black, and thick hair with a male pattern distribution, is one of the most common clinical manifestations of hyperandrogenism. Given that hirsutism is frequently treated prior to the patient receiving endocrinological evaluation, this may not be readily apparent. Women of East Asian descent or adolescents may experience it at much lower rates. Few doctors use standardized procedures (such the Ferriman-Gallwey score) for objective scoring, and normative data in large groups are still unavailable.

Another possible indicator of hyperandrogenism is the exclusive presence of acne, but perhaps not alopecia.

Measurements of free testosterone or the free androgen index (FAI), which is calculated by multiplying testosterone by 100 and dividing it by levels of sex hormone-binding globulin, are used to identify biochemical markers of hyperandrogenism. Equilibrium dialysis, total testosterone or ammonium sulfate precipitation are suggested techniques for measuring free testosterone. Free testosterone can also be calculated from measurements of sex hormone binding globulin and free testosterone. From a clinical standpoint, finding out the specific procedure employed in the neighborhood lab would be helpful. The absence of well-defined normative ranges, the high level of variability in the general population, the lack of information on teenagers, older women, and the various body mass index (BMI) ranges are all issues with androgen tests. The findings could potentially be impacted by hormone therapy before the measurement. For instance, the levels will decrease if you take an oral contraceptive.

1.1.6 Polycystic Ovaries

Both the patient and the clinician frequently become very confused as a result of this ultrasound-based diagnostic. The accepted definition is the existence of at least 12 follicles, each measuring 2 to 9 millimeters in diameter, and/or an increased ovarian volume (>10 milliliters) in each ovary. The rise in stromal echogenicity and volume, as well as the location of follicles, should be ignored. Women taking the oral contraceptive pill are not included by this definition. To diagnose, only one ovary that fits the criteria is needed. As ovarian morphology fluctuates throughout the menstrual cycle, it is ideal to undergo a transvaginal scan in the early follicular phase (between days 3-5). Estimate the volume of the ovaries in both the longitudinal and anteroposterior cross sections, using the formula 0.5 length breadth thickness and follicle number. It is possible to scan women with irregular periods at random or following progesterone-induced bleeding(Stankiewicz & Norman, 2006a).

1.1.7 Etiology Of PCOS

PCOS is undoubtedly a complex condition with an unknown origin but it also seems to be related to pro-inflammatory metabolic imbalance and biochemical abnormalities (Chan Hee Kim, 2O2O). Hormone asymmetries, insulin resistance (the body's inability to correctly use insulin), and excessive testosterone (the body's overproduction of testosterone) are the causes of PCOS's adverse effects. The endocrine ailment polycystic ovarian dysfunction (PCOS) has a convoluted pathophysiology. PCOS, which is characterized by weight, ovarian brokenness, and hormonal motors, is brought on by a combination of genetic and natural circumstances. Increased understanding of the issue has been impeded by the lack of adequate techniques for assessing either hyperandrogenism or insulin blockade. Insulin resistance is a pathophysiological feature in about half of PCOS patients, and hyperandrogenism is recognized in 60 to 80 percent of these patients. Solidity, both publically and through the amplification of PCOS, exacerbates philosophical misunderstandings with hyperandrogenism, hirsutism, intransigence, and parenting. While being overweight has an effect on the mental components of PCOS, obesity exacerbates the increased risk factors for impaired glucose tolerance, Diabetes Mellitus Type II, and Cardiovascular Disease. (Mehrukh Zehravi, Polycystic ovary syndrome and infertility: an update, July 22, 2021)

1.1.8 Environment and PCOS

A gene-centric explanation for the PCOS epidemic is oversimplified. The increase in PCOS in populations where the gene pool has remained largely stable is evidence that environmental influences are becoming more and more significant. In those who are vulnerable, the onset of PCOS is associated with the onset of obesity. Positive energy balance is common in developed countries due to the lowdaily energy expenditure and the plentiful and affordable food supply, but we argue that this is oversimplified and that other environmental factors, perhaps less well

known or recognized, may also play a role, such as exposure to infectious agents or environmental toxins(Legro et al., 2006a).

1.1.9 Epigenetics and PCOS

Since an epigenetic mechanism is typically involved in the development of various diseases in adulthood that are brought on by dietary or environmental variables in utero, it appears plausible that the same mechanism may also be present in PCOS. This theory postulates that prenatal exposure to hyperandrogenism may result in abnormalities in epigenetic reprogramming in the fetal reproductive tissue, which later manifest as the adult PCOS phenotype. Furthermore, transgenerational transmission of the PCOS phenotype is encouraged if these epigenetic changes continue in the germ cell line. It is obvious that other genetic variables (such as those connected to insulin resistance) and post-natal environmental factors (such as food) may have an impact on the phenotype of PCOS, possibly in conjunction with epigenetic anomalies. Foetal growth restriction and later risk of type 2 Diabetes Mellitus (DM) and cardiovascular disease are particularly linked, according to epidemiologic and clinical research mostly involving adult human populations. Elevated insulin resistance in young people exposed to a poor in utero environment and born small for gestational age (SGA) has been related to an increased risk for certain metabolic illnesses. These studies provide evidence for a general connection between fetal growth restriction, elevated adiposity, and insulin resistance beginning in the early years of childhood. Genetic variations may modify insulin resistance measures in SGA people in addition to fetal environmental variables. This may help to partially explain the varying levels of insulin resistance seen in individuals exposed to unfavorable in utero conditions. On the other hand, these fetuses' overnutrition may have long-term impacts on obesity, insulin resistance, and a propensity for glycemic control issues. Children of mothers who had diabetes when pregnant are more likely to be obese as children and to develop impaired glucose tolerance and type 2 DM sooner in life. Teenagers may be predisposed to PCOS by intrauterine adverse events that result in insulin resistance and/or hyperinsulinemia, given the action of insulin on modifying ovarian

and adrenal steroidogenesis. Overall, these studies suggest that at least some metabolic aspects of the PCOS phenotype, specifically the propensity for increased fat mass, visceral adiposity, and insulin resistance, are programmed in utero(Legro et al., 2006a).

1.2.1 Hormonal Association and PCOS

A study that looked at the relationship between PCOS and hormone levels among Pakistani people. Both affected and unaffected people are included in this cross-sectional investigation. Blood was taken for hormonal investigation using radioimmunoassay and immunoradiometric assay after a clinical examination was completed. They came to the conclusion that, as compared to healthy individuals, PCOS patients had significantly higher levels of BMI(Body Mass Index), FSH(Follicle Stimulating Hormone), LH(Luteinizing Hormone), and prolactin. The fundamental factors that must be taken into account for the diagnosis of PCOS are the levels of FSH, LH, and androgen. Increased androgen levels as a result of elevated LH cause the development of PCOS (Nida Ajmal, Polycystic ovary syndrome (PCOS) and genetic predisposition: A review article, July 2019).

1.2.2 Genetics and PCOS

PCOS is a highly complex and heterogeneous disorder. Despite variations between and within families the genetic cause of PCOS is linked to a common mechanism. A single gene or related genes in a single family have not been described due to complexity and heterogeneity.
Patients from the same family have varying genetic susceptibilities for various genes.
Intrauterine programming has recently been proposed as a PCOS susceptibility factor. It is implausible to use genome screening to look for a candidate gene in a disorder as complex as PCOS. In such families, linkage analysis consistently yields disappointing results. Case-control studies with a larger population size and genome-wide association studies (GWAS) are beneficial in identifying potential associations in such a condition. In these disorders, parental

analysis is In such families, linkage analysis consistently yields disappointing results. Case-control studies with a larger population size and genome-wide association studies (GWAS) are beneficial in identifying potential associations in such a condition. Parental analysis in these disorders is frequently impractical, but disease risk that is already known can be approximated (Paula Amato MD, October 2004)

1.2.3 Transgenerational Factors

Animal studies and human data demonstrate the syndromes transgenerational roots with daughters born to moms with PCOS having a 5 fold increased risk of inheriting the condition. In a mouse model an excess of prenatal androgen alone can increase the risk of PCOS being passed down through generations. Early exposure to androgens may make people more susceptible to the condition. Infant girls born to PCOS mothers have been reported to have longer anogenital distance (AGD), and daughters of PCOS mothers have higher metabolic and androgenic risk. It was discovered that maternal testosterone in PCOS-afflicted women was a predictor of newborn AGD. Although AMH (Anti Mullerian Hormone) may be a factor the exact process by which the daughters are exposed to hyperandrogenism is still unknown. It's interesting to note that a recent study found that mice exposed to high amounts of AMH in late pregnancy produced offspring with PCOS who had higher levels of androgen and luteinizing hormone pulsatility. The mechanism was believed to work by increasing aromatase activity in the placenta through the influence of AMH. Although it has been noted that women with PCOS had high amounts of AMH in the second and third trimesters, further research is needed to determine how AMH affects transgenerational transmission in people (Kathleen M Hoeger, 3, March 2021).

1.2.4 Types Of PCOS

There are four types of pcos.

Insulin- Resistant PCOS: The most typical form of PCOS is this one. Trans fat, sugar, pollution, and smoking all contribute to this kind of PCOS. In this, elevated insulin levels stop ovulation and cause the ovaries to start producing testosterone.

Pill- Induced PCOS: The second most typical kind of PCOS is this one. It develops as a result of birth control drugs that prevent ovulation. Most women experience these side effects briefly before returning to normal ovulation after the pill's influence wears off. But even when the effects of the tablets wear off, some women do not start ovulating again for months or even years. Women should see their doctor at that time.

Inflammatory PCOS: Ovulation is blocked, hormones become out of balance, and androgens are created due to inflammation in PCOS. Stress, pollutants in the environment, and inflammatory foods like gluten are the main causes of inflammation.

Hidden PCOS: This is a more straightforward variety of PCOS, and once the underlying reason is addressed, recovery typically takes three to four months. Thyroid condition, iodine deficiency (ovaries need iodine), vegetarian diet (it makes you zinc deficient and the ovaries need zinc), and artificial sweeteners are some of the causes of hidden PCOS. (Types of PCOS – What are PCOS Symptoms and Treatment, 2022)

1.2.5 Symptoms Of PCOS

The symptoms of PCOS may include:

- Missed periods, irregular periods, or very light periods, dysammenorhea.
- Ovaries that are large or have many cysts.
- Excess body hair, including the chest, stomach, and back (hirsutism).
- Weight gain, especially around the belly (abdomen).
- Acne or oily skin.

- Male-pattern baldness or thinning hair.
- Infertility.
- Small pieces of excess skin on the neck or armpits (skin tags).
- Dark or thick skin patches on the back of the neck, in the armpits, and under the breasts (Polycystic Ovary Syndrome (PCOS), n.d.).
- sleep apnea.
- Anxiety and depression (Nida Ajmal, Polycystic ovary syndrome (PCOS) and genetic predisposition: A review article, July 2019, 100060).

Figure 2 : PCOS Symptoms (Source -Flo health)

1.2.6 Clinical Diagnosis Of PCOS

An increased level of circulating total or bioavailable androgens, polycystic ovaries, and/or a history of oligomenorrhea and/or hyperandrogenism—most typically shown as hirsutism—clinically or biochemically. The 1990 NIH-NICHD conference's guidelines defined PCOS as unexplained hyperandrogenic persistent anovulation, effectively making it an exclusionary diagnosis. However, these ultrasound criteria for polycystic ovaries are also a moving target. The "consensus" definition did not include the polycystic ovary morphology, which is most frequently discovered today on ultrasound and consists of multiple 2–8 mm subcapsular preantral follicles and increased ovarian volume. These ultrasonography standards for polycystic ovaries, nevertheless, are likewise a moving objective. The updated 2003 Rotterdam diagnosis criteria now includes ultrasound criteria and calls for two of the three cardinal PCOS stigmata oligomenorrhea, hyperandrogenism, and polycystic ovaries.(Legro et al., 2006). Due to advancements in the resolution of pelvic ultrasonography, the International PCOS Network has proposed new criteria. They propose raising the cutoff point for the diagnosis of polycystic/multifollicular ovary to around 20 follicles per ovary. The team added that an ovarian volume more than 10 mL was consistent with PCOS. About all women with irregular menstrual cycles and hyperandrogenism show polycystic ovaries on ultrasound when the original ultrasound criteria is combined with an ovarian volume more than 10 mL. Sonographically discovered polycystic ovaries, despite they may signify a minor type of ovarian hyperandrogenism and insulin resistance, are insufficient as a single finding to diagnose PCOS (Robert L Barbieri, May, 2023). This was demonstrated in a study of 68 nonhirsute women, 39 of whom exhibited polycystic morphology on ultrasonography, and who had regular menstrual cycles. Women with polycystic morphology had greater levels of serum total and free testosterone as well as dehydroepiandrosterone sulfate (DHEAS) in the early follicular phase compared to those with normal ovarian morphology. Also, the women with polycystic morphology had greater fasting insulin levels and higher insulin resistance measured using a homeostasis model (fasting glucose x fasting insulin) (Robert L Barbieri, May, 2023).

Ovarian granulosa cells release AMH, a protein that belongs to the tumor growth factor family. At the antral stage of folliculogenesis, the largest AMH secretion takes place. The expression of aromatase, which is stimulated by the follicle stimulating hormone (FSH), is also inhibited by this glycoprotein hormone, which prevents the selection of a dominant follicle. It has been proposed that serum AMH concentrations, which are higher in PCOS-affected women, should replace ovarian ultrasound examinations. AMH cannot currently be used to diagnose PCOS in women or adolescents due to a lack of standardized tests and adequate normative ranges (Selma Feldman Witchel, 18 October 2019).

PCOS affects more than 80% of women who report with signs of androgen excess. A typical clinical manifestation of hyperandrogenism that affects up to 70% of women with PCOS is hirsutism. A modified version of the Ferriman-Gallwey scoring system is used to assess hirsutism. Seven areas of the body are assessed using this tool: the upper lip, chin/face, chest, back, belly, arms, and thighs. In the absence of terminal hair development, a score of 0 is assigned, and a score of 4 is provided for substantial growth. A sum of eight or higher indicates hirsutism. Ultrasound reveals polycystic ovaries in more than 90% of typically menstruating hirsute women. Additionally, 50% of women have PCOS, which has a milder distribution of unwelcome hair growth. Although it is less common in PCOS and less specific than hirsutism, acne can also be a sign of hyperandrogenism. Acne is found in 15% to 30% of adult women with PCOS. Because 5-reductase expresses differently in the sebaceous gland and the hair follicle, there is a larger concentration of dihydrotestosterone in the hair follicle, which may explain the difference in hirsutism and acne prevalence. Over 40% of the women who presented with severe acne were later found to have PCOS. Some specialists advise that women who arrive with acne be questioned about their menstrual history and checked for additional hyperandrogenic symptoms.

40% of PCOS-affected women struggle with infertility. The most frequent reason for anovulatory infertility is PCOS. Infertility clinics see between 90% and 95% of anovulatory women who have PCOS. Primordial follicle counts are normal in women with PCOS, while main and secondary follicle counts are much higher. However, as follicles attain a diameter of 4–

8 mm, follicular growth is stopped as a result of aberrations in components essential for normal follicular development. Ovulation does not occur because a dominant follicle does not form. Furthermore, occurrences of spontaneous abortion range from 42% to 73% in women with PCOS.

The National Institutes of Health/National Institute of Child Health and Human Disease (NIH/NICHD), the European Society for Human Reproduction and Embryology/American Society for Reproductive Medicine (ESHRE/ASRM), and the Androgen Excess and PCOS Society have all provided diagnostic criteria for PCOS. (Susan M Sirmans Department of Clinical and Administrative Sciences, 13 Dec 2022)

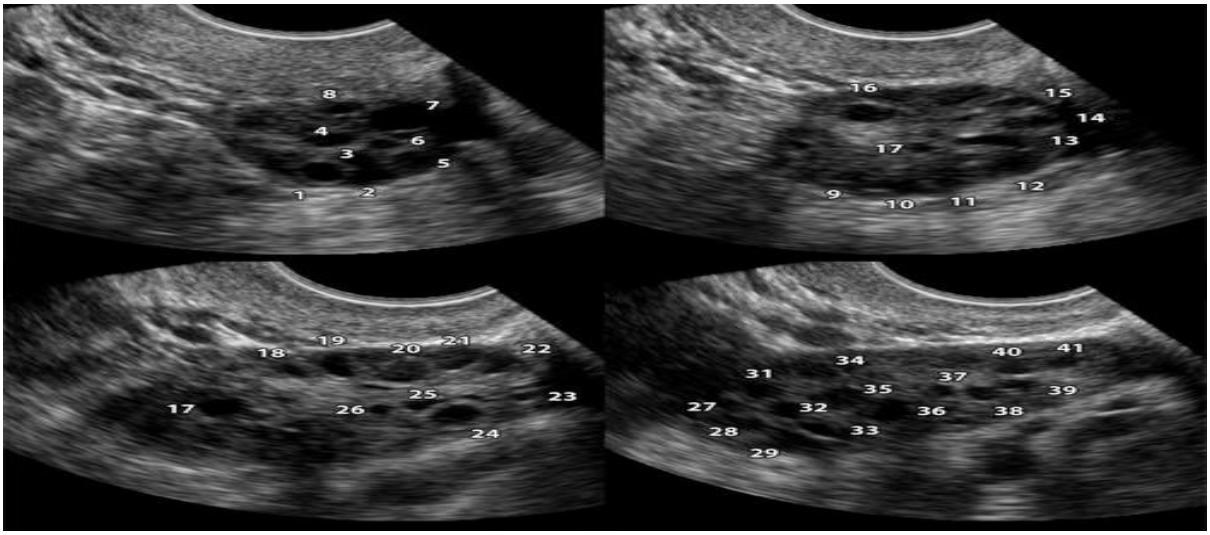

Figure 3: PCOS Diagnosis (Source – RSNA journals)

1.2.7 Pathophysiology

One of the most widespread endocrinopathies still lacks a thorough explanation of pathophysiology. However the definition of each contributory pathophysiological mechanism has taken a while to develop. The heterogeneity of PCOS may probably represent numerous pathophysiological causes(Tsilchorozidou et al., 2004). PCOS pathophysiology is a vicious cycle. The pathophysiology of PCOS is explained by a number of theories. One of these is the increased pulse frequency and amplitude of LH and relatively low FSH that result from neuroendocrine abnormalities. As a result, the generation of ovarian androgen is intrinsically flawed. A change in the metabolism of cortisol and an increase in the synthesis of the androgen adrenaline may also occur. Both directly and indirectly, through the reduction of hepatic SHBG production, insulin resistance with compensatory hyperinsulinemia further raises ovarian androgen production. Increased sympathetic nerve activity is linked to factors like obesity, insulin resistance, and high levels of androgens in the blood. In healthy females, androgens are secreted by the adrenal glands and ovaries in response to ACTH and LH, respectively. The production of androgen is divided roughly in half between peripheral enzymes in the skin, liver, and adipose tissue that convert 17-ketosteroids into androstenedione (predominantly) and direct secretion. Intraglandular autocrine and paracrine variables as well as other physiological parameters affect the production of androgen throughout the body. The hypothalamic-pituitary axis does not directly control androgen production in the adrenal glands. Although the adrenal glands contribute in about 30 to 50% of people who exhibit increased 17-ketosteroid responses to ACTH, the ovary is the primary source of androgen in women with PCOS. Unbalanced gonadotropin production, which includes excessive mean LH, low or normal FSH, and a chronically high frequency of GnRH pulse secretion, is a recurring characteristic of PCOS (Daniel A. Dumesic, 1 October 2015).

1.2.8 Obesity

In women with polycystic ovarian syndrome (PCOS), obesity affects nearly half of them. Epidemiological studies, which show that between 38% and 88% of women with PCOS are either overweight or obese, demonstrate the tight relationship between obesity and PCOS (Thomas M. Barber, 8 OCTOBER, 2020). PCOS-related obesity impairs reproduction in a number of ways. A key role is played by hyperandrogenism, elevated luteinizing hormone (LH), and insulin resistance. Leptin, adiponectin, resistin, and visfatin are among the compounds produced by adipose tissue that may be involved in the pathophysiology of PCOS (Ioannis E. Messinis MD, May 2015). Insulin resistance and compensatory hyperinsulinemia are linked to obesity. It has been demonstrated that insulin acts as a co-gonadotropin in culture to promote the generation of ovarian androgen. Leprauchaunism is one example of a strong insulin-resistant hyperinsulinemic state in women that has been linked to pronounced hyperandrogenemia. With insulin infusions to women with normal ovaries as well as when women with type 1 diabetes are treated with insulin, small elevations in circulating ovarian androgens have been seen. Lowered levels of circulating testosterone and higher ovulation rates have been linked to the use of anti-diabetic medications that boost insulin sensitivity or lower insulin levels. Obesity increases a number of additional growth and inflammatory variables that could either promote excessive ovarian androgen production or prevent androgens from aromatizing into estrogens (Richard S. Legro 1 Department of Obstetrics and Gynecology, 2012). Obesity and the prevalence of PCOS are closely associated; the prevalence is 4.3% in women with a body mass index (BMI) under 25 kg/m2 and 14% in those with a BMI over 30, however assessment bias could be at play (Kathleen M Hoeger, 3, March 2021).

1.2.9 Infertility

The cause of anovulatory infertility in more than 75% of instances is polycystic ovary syndrome. Although the exact cause of anovulation is unknown, there is evidence that the aberrant endocrine profile, namely the impact of insulin and LH on granulosa cell differentiation, is linked to the stalled antral follicle development. When it comes to management, antiestrogens can typically be used to induce ovulation. Treatment of clomiphene-resistant patients is challenging because standard gonadotropin dosages are linked to high incidence of multiple pregnancy and ovarian hyperstimulation syndrome. However, low-dose gonadotropin therapy has been shown to be successful in causing unifollicular ovulation. In this review, we describe a new examination of the findings from this center in detail. After six cycles, the overall conception rate was above 50%, and more significantly, the multiple pregnancy rate was just 3%. In obese PCOS patients, losing weight not only enhances the likelihood of getting pregnant, but it may also improve the long-term prognosis for developing diabetes. Metformin and other insulin-sensitizing medications may also be used to treat PCOS (Anwen Gorry, August 2006).

1.3.1 Diabetes

Despite the fact that PCOS is primarily an androgen excess illness, many individuals have insulin resistance and compensatory endogenous hyperinsulinemia that are closely linked to obesity and abdominal adiposity (Héctor F. Escobar-Morreale, Type 1 Diabetes and Polycystic Ovary Syndrome: Systematic Review and Meta-analysis, MARCH 15 2016). When the less strict WHO criteria are applied, studies of sizable cohorts of PCOS-affected women in the U.S. have shown that the prevalence rates of glucose intolerance in PCOS women can reach as high as 40%. These studies are noteworthy because they have revealed essentially equal rates of type 2 diabetes and impaired glucose tolerance in a population with a wide range of racial and geographic diversity. Based on 2-hour glucose-challenged glucose levels, the undiagnosed diabetes rate in these cohorts is around 10%. However, we have also seen PCOS teenagers with

impaired glucose tolerance or type 2 diabetes as well as thin people (body mass index 25) with glucose intolerance. The bulk of affected women are in their third and fourth decades of life. It can be inferred that PCOS contributes to about 20% of impaired glucose tolerance and 40% of type 2 diabetes in reproductive-aged women based on the prevalence of glucose intolerance in the U.S. population. Based on glucose levels measured after two hours of glucose challenge, these cohorts have an undiagnosed diabetes rate of 10% or less. However, we have also observed slim individuals (body mass index of 25) with glucose intolerance as well as PCOS adolescent patients with impaired glucose tolerance or type 2 diabetes. Women in their third and fourth decades of life make up the majority of those impacted. Based on the incidence of impaired glucose tolerance in the U.S. population, it can be assumed that PCOS causes 20% of impaired glucose tolerance and 40% of type 2 diabetes in reproductive-aged women. More aggressive diagnosis and treatment of this illness in PCOS women would be supported by a natural history that supports a significant worsening of glucose tolerance. Impaired glucose tolerance (IGT), with an average conversion rate of 1%–5% every year, is a risk factor for the onset of type 2 diabetes in other populations. Other groups of women are undoubtedly more susceptible to type 2 diabetes than others. For example, Latina women with a history of prenatal diabetes may experience a cumulative conversion rate to diabetes of up to 50% over the course of five years, or 10% annually (M.D., July 2006).

1.3.2 Insulin Resistance

One of the main symptoms of PCOS is insulin resistance, especially in women who have persistent anovulation and hyperandrogenism(Condorelli et al., 2018). Burghen et al. noted in 1980 that PCOS-affected women showed elevated insulin responses during oral glucose tolerance testing that could not be explained by obesity. Additionally, women with typical PCOS had acanthosis nigricans, indicating the likelihood that they shared the unusual symptoms of high insulin resistance with women who did not (Evanthia Diamanti-Kandarakis, Insulin Resistance and the Polycystic Ovary Syndrome Revisited: An Update on Mechanisms and Implications, 1

December 2012). Hyperinsulinemia, which occurs from resistance to insulin's effects on glucose metabolism, appears to be a significant extrinsic component in many PCOS cases. By revealing hidden anomalies in the regulation of steroidogenesis, the rise in insulin levels may cause hyperandrogenemia in genetically predisposed individuals. A polycystic ovary gene, which manifests in male pattern baldness, may be one of them. One of the many elements that interact with androgen to control the development of pilosebaceous units appears to be insulin. It is unknown whether treating PCOS with antidiabetic insulin-lowering drugs can help the disorder's pilosebaceous unit symptoms, though it may enhance ovarian function and androgen levels (Robert L. Rosenfield MD Section of Pediatric Endocrinology, September 2001).

1.3.3 Acne

The most prevalent endocrine condition in women is polycystic ovary syndrome (PCOS), which has an incidence of 6–8%. Acne is a common manifestation of hyperandrogenemia (Sayera Begum, (2012)January - March). A common symptom of PCOS is acne vulgaris (AV), which can aggravate the condition for about 62 percent of patients during adolescence. (G. Acmaz, 07 Apr 2019). The face, neck, upper back, and pectoral regions are where acne is most frequently seen. Acne is a condition of the pilosebaceous unit. Acne formation is influenced by androgens. The enzyme 5'-reductase transforms testosterone into the more potent androgen dihydrotestosterone in the sebaceous gland. Androgens also cause aberrant desquamation in follicular epithelial cells, which contributes to increased sebum production from sebaceous glands and increases comedone formation. Papules and pustules may appear after bacterial colonization of comedones (Servet Hacivelioglu a, October 2013).

1.3.4 Hirsutism

Excess terminal hair, or hirsutism, frequently manifests in a male pattern in females. Despite the fact that hyperandrogenemia is typically linked to hirsutism, 50% of women with mild symptoms have normal androgen levels. Three out of every four occurrences of hirsutism are caused by polycystic ovarian syndrome, which is also the most frequent cause (DAVID BODE, FEB 15, 2012). While hirsutism affects roughly 4–11% of women in the general population, it is the primary sign of hyperandrogenism in PCOS-affected women, with a prevalence of 6–75%. Both an excess of androgen and a person's unique reaction of the pilosebaceous unit to androgens are linked to hirsutism in PCOS. In clinical practice, the modified Ferriman-Gallwey (mFG) scoring method is frequently used to visually grade abundant terminal hair, standardizing the assessment of hirsutism and enabling data comparability. Although a common mFG score cutoff would be helpful for comparisons, ethnic differences, skin type, and other aspects should be taken into account when assessing hirsutism in various groups. The degree of hirsutism, as determined by standard methods of measuring androgen levels, has been demonstrated to have weak correlation. While the majority of women with PCOS and hirsutism also have serum androgen levels above reference levels, some of them could not exhibit biochemical hyperandrogenism, making the diagnosis of PCOS difficult (Prof. Poli Spritzer, 9 August 2022).

1.3.5 Alopecia

Excess androgen levels rise in the body, which is one of the main causes of pattern hair loss in polycystic ovary syndrome. Women’s ovaries, adrenal glands, and fat cells all naturally create androgens. These androgens have a part in regulating blood loss during menstruation as well as encouraging pubic and underarm excessive hair growth.Cysts develop in the ovaries in PCOS, which causes the body’s androgen levels to spike. More hair is forced into the telogen stage as cytokines are produced more frequently which damages the derma papilla. The damaged hair starts to cease growing altogether and gets shorter and thinner in diameter. DHEA and DHT are

two other hormones that cause hair loss in addition to this.
Diffuse hair loss is the typical outcome, which typically begins at the triangle-shaped frontal scalp midline and spreads to the sides and front of the scalp. One of the reasons baldness is uncommon in women with alopecia areata is because the frontal hairline is unaffected. (M.B.B.S., September 13, 2022).

1.3.6 Dysmenorrhea

According to the definition of dysmenorrhea, it is menstrual pain that occurs during ovulatory cycles and is brought on by myometrial contractions when there is no pelvic condition that could be causing belly pain. Primary dysmenorrhea is typically thought to be caused by prostaglandin activity, a vasoconstrictor that induces ischemic discomfort in the uterus. Primary dysmenorrhea is a common condition, although it is commonly misdiagnosed and poorly managed. Finding the key dysmenorrhea risk factors may help put women into groups that require vigilant monitoring or quick pain relief (Jee Young Jeong1, 22 July 2019). Pelvic discomfort, which normally occurs along with the menstrual flow but can occasionally arrive just before it, is a defining feature of the painful menstrual condition known as dysmenorrhea. When the blood flow is heavier, which occurs in the first few days of the menstrual cycle, the discomfort is at its most intense. It is a common gynecological issue. At some point during their reproductive years, 60% to 80% of women will experience menstrual discomfort. 8% to 18% of these women report feeling so uncomfortable that it interferes with their daily activities. Several unwelcome symptoms in women might occur during their menstrual cycle. Lower abdominal pain is the most typical.(Prevalencia et al., n.d.)

1.3.7 Hyperprolactinemia

The two endocrine conditions that affect women of reproductive age most frequently are polycystic ovarian syndrome (PCOS) and hyperprolactinemia (HPRL) (Clémence Delcour,

September 9, 2019). The most prevalent endocrine etiologies of anovulation in women are hyperprolactinemia and PCOS. Old studies that used non-conformist criteria to diagnose PCOS and that did not thoroughly (Delcour et al., 2019)examine hyperprolactinemia in light of current understanding are the source of the association between the two conditions. The steady development of MRI methods has made it possible to find tiny adenomas. It's interesting to note that the Endocrine Society guidelines advised PCOS patients to consider a pituitary MRI and screen for reasons of hyperprolactinemia. Furthermore, data from the literature indicate that there is no link between PCOS and hyperprolactinemia once other causes like prolactinoma, drug-induced hyperprolactinemia, pregnancy, hypothyroidism, chronic renal failure, cirrhosis, chest wall lesions, and breast stimulation have been thoroughly investigated in these women with hyperprolactinemia. Additionally, a new study shows that PCOS women frequently have elevated prolactin associated to the presence f a macroprolactin, making it critical to check for this condition. Therefore, limiting misclassification is crucial in order to prevent the unwarranted prescription of a pituitary MRI or even a dopaminergic agonist medication as was already mentioned in a previous study from years ago. In 2007, Filho established unequivocally that there was no hyperprolactinemia associated with PCOS when the etiology of the condition was thoroughly investigated(Hussein et al., 2020).

1.3.8 Cancer

Endometrial cancer risk is 2.7 times higher in women with polycystic ovarian syndrome (PCOS). The extended exposure of the endometrium to unopposed estrogen caused by anovulation is a significant contributor to this increased risk of developing cancer. Additionally, progesterone resistance and deregulation of genes governing steroid activity and cell proliferation can be seen in the secretory endometrium of some women with PCOS who are having their ovulation induced or receiving exogenous progestin. Transvaginal ultrasound and/or endometrial biopsy are used as part of endometrial surveillance to detect atypical vaginal bleeding, extended

amenorrhea, unopposed estrogen exposure, or thicker endometrium. A levonorgestrel-releasing intrauterine device (Mirena) or cyclic or continuous progestins are the main types of medical treatment for abnormal vaginal bleeding or endometrial hyperplasia. Treatment of obesity as a coexisting risk factor for developing endometrial disease should include calorie control and exercise. Some women with PCOS may also have a higher than average risk of developing ovarian cancer. Strong evidence suggests that oral contraceptive use protects against ovarian cancer and that this protection increases with the length of medication. The inhibition of gonadotropin secretion rather than the avoidance of "incessant ovulation" may be the mechanism through which this protection is provided. The two major medical treatments for abnormal vaginal bleeding or endometrial hyperplasia are a levonorgestrel-releasing intrauterine device (Mirena) and cyclic or continuous progestins. Exercise and calorie restriction should be used to treat obesity as a concomitant risk factor for developing endometrial disease. Ovarian cancer may be more likely to strike some PCOS patients than other women. There is compelling data that suggests oral contraceptive use reduces the risk of ovarian cancer and that this risk reduction increases with the duration of the prescription. The prevention of "incessant ovulation" may not be the method by which this protection is offered, but rather the inhibition of gonadotropin secretion (Daniel A. Dumesic a, August 2013).

1.3.9 Heart Disease

Cardiovascular risk factors are more common in adolescents and women of childbearing age who have PCOS. Compared to controls of the same age, there is enough evidence to support the existence of subclinical atherosclerosis in women with PCOS. Few prospective studies, however, have looked at both fatal and nonfatal cardiac events in women with clearly characterized PCOS (Dokras, August 2013). In 1985, Wild and colleagues discovered that compared to women who

had regular periods, those with PCOS had lower HDL levels, higher LDL/HDL ratios, and higher triglyceride levels. Recent studies by Slowinska-Srzednicka et al. have highlighted the involvement of insulin in the aberrant lipid levels found in hyperandrogenic PCOS women. These researchers compared 22 eumenorrheic control patients who were neither obese nor not with 27 PCOS-afflicted women. Women with PCOS exhibited higher triglyceride levels and noticeably decreased HDL levels. After adjusting for age, body mass index (BMI), and sex steroids, multiple regression analysis in PCOS patients showed that fasting insulin was a significant explanatory variable for total triglyceride and apoA-1 levels. These findings are supported by a 1992 study by Wild et al in which 31 women with evidence of androgen excess were treated for 3 months with a gonadotropin-releasing hormone agonist that suppressed ovarian estradiol and testosterone. These results suggest that hyperinsulinemia independent of obesity may play a role in the lipid disturbances in PCOS. Despite the reduction of sex steroids, abnormal lipid profiles persisted and were still linked with insulin resistance. It was determined9 that insulin seemed to be more closely linked to aberrant lipoproteins than to endogenous androgens or estrogens (Evelyn Talbott, 1 Jul 1995).

1.4.1 Autoimmune Disease

In essence, PCOS is a hormonal condition that is supported by hyperandrogenism and insulin resistance. Mezaal et al. recently demonstrated that insulin plays a direct or indirect role in the synthesis of sex hormones. By using gene sequencing, they discovered several INS gene insertions, deletions, and substitutions in PCOS patients. They hypothesized that insulin resistance can negatively impact sexual function and may even be the root cause of PCOS. Despite being recognized as an autoimmune disorder, the pathophysiologic relationship between PCOS and type 1DM (Type 1 Diabetes Mellitus) has not yet been demonstrated. Exogenous insulin used to treat type 1 diabetes has been linked to PCOS development in individuals, according to research. Exogenous insulin that is supplied non-physiologically may encourage the ovaries to produce androgens. According to Codner et al., intensive insulin therapy may be to

blame for PCOS in females with type 1 diabetes. In patients with type 1 diabetes, they reported significant rates of hyperandrogenism and PCOS, which seem to be related to vigorous exogenous insulin administration.

ANA and anti-TPO, which have been linked to systemic lupus erythematosus and Hashimoto thyroiditis, respectively, are associated with PCOS, and it is hypothesized that these autoantibodies may affect the long-term clinical management of these patients. As a result, variations in autoantibody levels across PCOS patients provide us with a new avenue for future molecular research. This could eventually lead to the development of more effective PCOS treatment alternatives.

Since PCOS patients have thyroid autoimmune signs, PCOS patients should have their thyroids checked for these indicators. Furthermore, changes in the levels of the hormones estrogen, progesterone, and thyroid are known to cause gynecological issues that may ultimately result in fetal loss and the development of endometrial, ovarian, and breast malignancies(Mobeen et al., 2016).

1.4.2 Pregnancy Complications

Early pregnancy loss (EPL), gestational diabetes (GDM), pregnancy-induced hypertensive disorders (PET/PIH), and the delivery of small for gestational age (SGA) newborns are pregnancy complications linked to maternal PCOS. Obesity, hyperinsulinemia, high luteinizing hormone concentrations, and endometrial dysfunction have all been linked to an increased risk of EPL. An above-average result of gestational diabetes in PCOS women would be expected, given the high incidence of obesity and insulin resistance among these women. When this was investigated by estimating the incidence of gestational diabetes among pregnant women with PCOS, it did indeed turn out to be the majority opinion. Pregnancy as the trigger may be expected to result in an increased incidence of pregnancy-induced hypertension (PIH) and pre-eclamptic toxemia (PET), as hypertension is now well recognized as a probable sequela of PCOS

over the age of 40, especially in those who are obese and insulin-resistant (Medicine), June 2006).

1.4.3 Mental Disorder

It is uncertain whether there is a causative connection between PCOS and psychiatric illnesses(Jin et al., 2021). The notion that is currently being discussed the most centers upon prenatal exposure to increased androgen levels. Additionally highlighted is the part epigenetic factors play in PCOS development during adolescence and adulthood. A third explanation is that PCOS is caused by a genetic condition, most likely a gene polymorphism. An intriguing finding is the occurrence of specific PCOS symptoms in the sisters of PCOS patients, which occur between 22 and 32% of the time and fulfill PCOS diagnostic criteria. There is additional data that suggests polycystic ovarian syndrome has a male counterpart. For instance, androgenic alopecia and a poor metabolic profile are more common among the brothers and dads of PCOS patients. According to a still-relatively small number of research, women with PCOS have a higher frequency of a number of psychiatric problems. These include eating disorders, obsessive-compulsive disorder, obsessive-generalized anxiety disorder, personality disorders, social phobia, and attention deficit hyperactivity disorder (ADHD). More frequently than in the general population, women with PCOS have also been documented to have bipolar affective disorder, schizophrenia, and other psychotic diseases. This article aims to give a summary of the research on mental illnesses in women with polycystic ovarian syndrome.

The frequency of attention deficit hyperactivity disorder in women with polycystic ovarian syndrome is currently a subject of very few papers. In one study which included 40 women with PCOS and 40 healthy controls, scores on the adult ADHD scale were considerably higher in the PCOS group. The Wender-Utah Rating Scale was also used to determine that the PCOS group had a higher incidence of childhood ADHD than the control group.

In 1993, researchers discovered the first link between heightened levels of testosterone and

luteinizing hormone and psychotic illnesses. In 2011, researchers looked into the parallels between the development of polycystic ovarian syndrome and schizophrenia. 96 studies on PCOS and schizophrenia were considered. It was found that the comorbidity of both illnesses was predicted by insulin resistance and high testosterone levels. The Swedish study also revealed that women had an 82% higher incidence of schizophrenia(Rodriguez-Paris et al., 2019).

1.4.4 Obstructive Sleep Apnea

This condition is more prevalent in PCOS and is not only attributable to fat. Age, BMI, and levels of circulating testosterone appear to be less accurate predictors of sleep disordered breathing than insulin resistance(Stankiewicz & Norman, 2006).

1.4.5 Treatment and Management Of PCOS

Since none of the currently available drugs have been completely able to prevent these effects, polycystic ovarian syndrome (PCOS) continues to pose a challenge to clinical and fundamental research scientists (Lekha Saha, 07 January 2011). The best way to treat and control PCOS is mostly by pharmacological therapy, lifestyle changes, surgery, and other treatments like laser therapy. There is currently no known permanent cure for PCOS.

1.4.6 Pharmacological Therapy

Metformin

The most extensively researched and frequently used medication for the treatment of pcos is metformin. Biguanide metformin primarily treats type 2 diabetics for hyperglycemia and has direct effects on the insulin signaling system. Specifically, it reduces glycogenolysis, inhibits gluconeogenesis both directly and indirectly (by lowering free fatty acid concentrations), increases peripheral glucose uptake by skeletal muscle and adipose tissue, and decreases intestinal glucose absorption. Metformin has been shown to enhance insulin sensitivity in PCOS patients, alleviating both hyperinsulinism and hyperandrogenism. When used continuously during pregnancy, it has also been shown to reduce the risk of gestational diabetes from 30% to 3%. Furthermore, moderate to severe hirsutism in PCOS-affected females is thought to be treatable with metformin. Furthermore, using metformin for three months caused a 14% decrease in the acne score. The lipid profile has also been demonstrated to benefit from metformin, with minor increases in high-density lipoprotein (HDL) cholesterol and decreases in triglycerides or low-density lipoprotein (LDL) cholesterol. Slight weight reduction, a lower BMI, and a smaller waist-to-hip ratio have all been observed in a number of studies testing metformin therapy for PCOS. However, other people have reported decreasing insulin resistance without a corresponding decline in body fat. Metformin has gynecological benefits in addition to metabolic advantages. Metformin has been shown to reduce androgen production in women with PCOS both directly by impacting ovarian thecal cells and indirectly by raising SHBG levels. Menstrual cyclicity can resume normally as a result of the lowered amounts of androgen(Katsiki et al., n.d.).

Clomiphene

The medication used to induce ovulation most frequently prescribed is clomiphene citrate. It is the first-choice treatment for normogonadotrophic oligo/amenorrheic infertility (WHO group 2), which is primarily characterized by polycystic ovaries. At least six cycles of treatment, and ideally no more than 12 cycles, should be given to anovulatory women who respond to clomiphene citrate. Due to the danger of multiple pregnancies and the patients' varied reaction to various clomiphene doses, at least the first cycle must be monitored by ultrasonography. Additionally, one must not undervalue the danger of ovarian hyperstimulation syndrome. Ovulation inducement produces more triplets and higher order pregnancies than in vitro fertilization, and multiple pregnancies carry a number of dangers for both the mother and the unborn child. The current results are inconclusive about the use of empirical clomiphene in the management of unexplained infertility (Nasseri, 03 Jul 2009).

Letrozole

An oral aromatase inhibitor with strong potential for ovulation induction is letrozole. This chemical has been investigated as a potential ovulation inducer by numerous researchers, and it has been in use for a few years now. Letrozole works by preventing the conversion of androgens to estrogens, which lowers estrogen production. Additionally, it has no negative effects on cervical mucous or endometrium. In PCOS women who are resistant to CC (clomiphene citrate), letrozole has been demonstrated to have a decent ovulation rate. Women with PCOS are more prone to have significant CC resistance due to the high incidence of insulin resistance. In such women, letrozole may show to be a beneficial substitute for ovulation induction (Kar, 2012 Sep-Dec).

Orlistat

Ovulation disorders are the primary cause of infertility in women with PCOS, and obesity is another factor that contributes to the poor fertility that is linked to monthly irregularities, androgen excess, hyperglycemia, IR, and dyslipidemia. Body weight, waist circumference, BMI, and waist-to-hip ratio (WHR) are typical indicators of a person's body fat percentage. WHR is a crucial benchmark to assess central obesity, although BMI is a widely used, trustworthy scientific index. A meta-analysis of 23 clinical studies with 941 individuals examined the efficacy of metformin, inositol, liraglutide, and orlistat in helping PCOS women who are overweight or obese lose weight. After receiving treatment for 12 weeks, only orlistat significantly decreased individuals BMI but waist circumference showed no improvement, according to subgroup analysis. 100 obese PCOS patients of reproductive age participated in a double-blind, randomized, placebo-controlled trial. They were randomly assigned to orlistat or placebo groups. Every participant followed the same low-calorie diet and exercised for 30 minutes each day. When compared to the control group and before treatment, the intervention groups weight, BMI, and WHR had dramatically decreased after 3 months of therapy. 101 obese PCOS patients (BMI 34.5 5.9 kg/m2) and 29 obese women with regular menstrual cycles participated in a prospective trial where all subjects were given a low-calorie diet and exercised to the proper intensity. Body weight, BMI, and WHR in the PCOS and control groups had all significantly decreased after 6 months of orlistat therapy; however, there had been no discernible difference in the rates at which the BMI and WHR had decreased between the groups (Shi, 19 December 2018).

Isotretinoin

The most prevalent endocrine condition in women is polycystic ovary syndrome (PCOS), which has an incidence of 6–8%. Approximately 62 percent of PCOS patients will experience

complications during adolescence due to the well-known PCOS characteristic known as acne vulgaris (AV). (G. Acmaz L. C., 07 Apr 2019). Isotretinoin works by decreasing sebum production, preventing the growth of bacteria and cells, inducing cell differentiation and apoptosis, regulating the development of microcomedones, preventing the growth of lesions and pre-existing comedones, and restoring normal desquamation of the epithelium. Additionally, it might have anti-inflammatory properties. There is mounting evidence that the main mechanism of action of isotretinoin in acne is sebocyte apoptosis, which suppresses sebum production.

Statins

The use of statins is another area where there is growing evidence in the literature for a cardiovascular and endocrine benefit in women with PCOS. They have been demonstrated to lower inflammation, enhance lipid profiles, and treat hyperandrogenemia. However it is unknown if long-term use of these medications will prevent cardiovascular disease in young PCOS women. The use of this medication in women of reproductive age raises questions about teratogenicity because it is under FDA pregnancy category X. These medications are still being tested in PCO women(*Natural Molecules for the Therapy of Hyperandrogenism and Metabolicdisorders in PCOS*, n.d.)

Inisitol

The insulin sensitizing activity of inisitol which reduces insulin resistance is a significant effect it has on PCOS patients. In the treatment of obese PCOS women, inositol enhanced ovulatory function, boosted insulin action, and reduced serum androgen, blood pressure, and plasma triglyceride levels. While some research show that inositol medication considerably lowers BMI. Some of the positive effects of inisitol were muted in patients who were severely obese (BMI > 37 kg/m2) and there was an inverse correlation between therapy and BMI(Kamenov & Gateva, 2020).

Oral Contraceptive Pill (OCP)

OCP or combined oral contraceptives are frequently recommended to treat PCOS symptoms. OCPs comprise both an estrogen derivative and a progestogen that work largely by thickening cervical mucus and inhibiting ovulation via negative feedback to the brain. Contraceptive medication has been shown to considerably lessen the hyperandrogenic symptoms in PCOS patients and restore the proper menstrual cycle. However data gathered from clinical experience shows that extended OCP therapy might have adverse effects, which can range from a simple increase in weight to changes in cardiometabolic indices. In light of these findings, either the prescription of OCPs with various anti androgenic potential or the investigation of other treatments is the therapeutic strategy chosen(Treatment of Lean PCOS Teenagers: A Follow-up Comparison between Myo-Inositol and Oral Contraceptives, n.d.).

Spironolactone

For most PCOS symptoms, such as hirsutism, acne, seborrhea, and effluvium capillorum, treatment with 100 or, less frequently, 200 mg of SPironolactone daily for 6 to 9 months is quite beneficial. In most individuals, the results last even after the patient stops taking the medication. The complicated antiandrogen activity of spirolactone may be responsible for this finding's explanation (Decio Armaninia, 28 July, 2016).

Folic Acid

The metabolic profiles of PCOS-afflicted women can significantly benefit from daily folic acid intake. Because it supports the fetus's proper growth, folic acid is a prenatal vitamin that should

be taken both before and during pregnancy. In instance, folate aids in the prevention of spina bifida and other neural tube disorders. In 60% of women, taking daily supplements of folic acid and inositol can increase insulin sensitivity and encourage ovulation (Saharkhiz, 2021).

Flutamide

Another non-steroidal anti-androgen that has been demonstrated to be beneficial against hirsutism in smaller trials is flutamide, an androgen-receptor agonist. The most frequent side effect is dry skin, however hepatitis has occasionally been linked to its use. Due to the considerable teratogenic risk associated with this substance, contraception should be taken. For the treatment of PCOS flutamide has also been used with dietary changes and metformin medication, and these combinations may have additive effects(Natural Molecules for the Therapy of Hyperandrogenism and Metabolicdisorders in PCOS, n.d.).

Vitamin E

Tocopherol generally known as vitamin E, is a lipid-soluble compound that has non-enzymatic antioxidant capabilities. It was first discovered by Evans and Bishop in 1922. Vitamin E is frequently utilized in the field of reproductive medicine because it has the ability to effectively counteract the negative effects that oxidative stress has on the endocrine and reproductive systems. Through reducing the activity of phospholipase, vitamin E, which is crucial for the entire process of reproduction, can combat the oxidative stress brought on by oxygen free radicals and an imbalance of antioxidants. Vitamin E's anti-oxidant capabilities can help to lessen the senile oxidative stress response, which could negatively impact the quantity and quality of oocytes. Infertility in women, miscarriages, early deliveries, eclampsia, fetal intrauterine development restriction, and other pregnancy-related illnesses can all be brought on by a deficiency of vitamin E(Chen et al., 2020).

Vitamin D

Women with polycystic ovarian syndrome (PCOS) frequently have vitamin D deficiency, with blood values of 25-hydroxy vitamin D (25OHD) 20 ng/ml in 67–85% of PCOS patients. With observational studies revealing that lower 25OHD levels were linked to insulin resistance, ovulatory and menstrual abnormalities, decreased pregnancy success, hirsutism, hyperandrogenism, obesity, and higher cardiovascular disease risk factors, vitamin D deficiency may exacerbate symptoms of PCOS. There is some, but not much, evidence that vitamin D supplementation has positive benefits on insulin resistance and menstrual dysfunction in PCOS-affected women (Rebecca L. Thomson, 10 May 2012).

1.4.7 Surgical Treatments

Ovarian Drilling

If lifestyle changes and medication have been tried without success, this surgery might enhance the likelihood of ovulation. If PCOS patients are having trouble getting pregnant this treatment may be better than taking medication. Not all professional societies advise the treatment. A small incision is made in your belly for ovarian drilling, and a laparoscope—a long, thin instrument—is inserted. A little portion of the ovary is then punctured and destroyed by the surgeon using an electric current-equipped needle. Lower testosterone levels as a result of the operation could enhance ovulation. This procedure does not appear to raise the chance of multiple pregnancies and may be less expensive than gonadotropin-based treatment. However, there is a chance that it will scar the ovaries (Treatments for Infertility Resulting from PCOS, 2017).

Bariatric Surgery

Bariatric surgery is one of the best ways to treat obesity and its associated comorbidities. Potentially new indications for bariatric surgery include PCOS and endometrial hyperplasia (EH), which are linked to an increased risk of endometrial cancer. The three main bariatric treatments are laparoscopic adjustable gastric banding, laparoscopic sleeve gastrectomy, and Roux-en-Y gastric bypass. When properly chosen and carried out by skilled bariatric surgeons, these well-established treatments can result in significant weight loss and the remission of obesity-related comorbidities. According to studies, bariatric surgery can help patients with PCOS control their condition and increase fertility. Likewise bariatric surgery reduces endometrial hyperplasia, making medically induced weight loss a potentially appealing alternative for the prevention and treatment of endometrial cancer. Obesity has a negative effect on fetomaternal outcomes, assisted reproduction techniques, and naturally occurring pregnancies. Obese women with subfertility can spontaneously become pregnant after bariatric surgery. However, despite the fact that bariatric surgery lowers the risk of preeclampsia and gestational diabetes, there is a potential rise in the risk of stillbirth or neonatal mortality as well as an increased risk of small for gestational age (Vasileios Charalampakis, December 2016).

In Vitro Fertilization(IVF)

As a third-line therapy (following the failure of first- or second-line therapies such as clomiphene citrate, metformin, or ocp) or when there are additional infertility factors present, such as tubal damage, severe endometriosis, or male factor infertility, IVF treatment is advised for anovulation alone in women with PCOS. When receiving IVF therapy, women with PCOS experience pregnancy, miscarriage, and live birth rates that are comparable to those of non-PCOS patients (Michael F. Costello, 28 May 2012).

1.4.8 Other Treatments

Laser Therapy

Women with hirsutism typically have PCOS, which has been regarded as the most prevalent diagnosis. The most upsetting manifestation of hyperandrogenism in women with PCOS is, by far, facial hirsutism. Patients with PCOS who received laser-assisted hair removal reported a statistically significant improvement in their psychological well-being. The principle of selective photo thermolysis has revolutionized laser hair removal because, when used by adequately qualified and experienced specialists, it is both efficient and secure (Chun-Man Lee Department of Dermatology, 08 Dec 2017).

1.4.9 Lifestyle Modification

Weight loss, dietary changes, and physical activity ought to be the gold standard for enhancing insulin sensitivity in obese PCOS women. Unfortunately, there are no treatments that are effective enough to provide lasting weight reduction, and it is predicted that 90–95% of people who do lose weight will regain it. Additionally, bariatric surgery is the only form of treatment that causes a persistent and significant weight loss in those who are obviously obese. According to current National Institutes of Health recommendations, patients with a BMI of 40 or higher or with a BMI of 35 or higher and significant medical comorbidities should consider having bariatric surgery. Whether PCOS counts as a serious comorbidity is up for debate. Women with PCOS seem to notice a significant reduction in symptoms after surgery, suggesting that in some cases, this may be a cure for the syndrome. These findings, however, are essentially case studies and require more validation in follow-up research(*Natural Molecules for the Therapy of Hyperandrogenism and Metabolicdisorders in PCOS*, n.d.).

A review on Polycystic Ovary Syndrome (PCOS) Epidemiology, Symptoms, Diagnosis, Risk Factors & Treatment

Chapter two
Purpose of the study

2.1 Purpose of the study

PCOS is a syndrome that alters how ovaries function and causes hormonal imbalances in women of all ages, but especially in those who are approaching childbearing age. One in every ten

women of reproductive age has PCOS.

PCOS cannot be completely cured, however it can be managed.

- To understand what pcos really is.
- current global prevalence of pcos.
- To be familiar with the underlying causes and symptoms of pcos.
- To be able to diagnose pcos.
- To be aware of the pcos risk factors.
- To know about the treatments of pcos and lifestyle modification that can help in the management of pcos.

Chapter three
Literature Review

A review on Polycystic Ovary Syndrome (PCOS) Epidemiology, Symptoms, Diagnosis, Risk Factors & Treatment

3.1 Literature Review

Male sex hormones, which are typically present in modest amounts in healthy males, are abnormally produced by the ovaries in PCOS. The multiple tiny cysts that develop in the ovaries are referred to as polycystic ovarian syndrome. It is unclear what causes pcos specifically. But pcos is influenced by genetics. Pcos is caused by a number of different variables, including the environment, hormonal associations, epigenetics, and transgenerational influences. The prevalence of pcos is rising worldwide. Long, painful, missed periods, acne, obesity, insulin resistance, hirsutism, infertility, weight gain, sleep apnea, anxiety, and sadness were all signs of pcos. Rotterdam criteria are used to diagnose PCOS after ruling out two of the three conditions- anovulation, hyperandrogenism, and polycystic ovaries. For the diagnosis of pcos, additional tests are carried out, including ultrasonography, lipid profile checks, fasting glucose levels, prolactin hormone levels, anti-mullerian hormone levels, follicle stimulating hormone levels, testosterone levels, etc. Obesity, infertility, diabetes, insulin resistance, acne, hirsutism, alopecia, dysmenorrhea, hyperprolactinemia, cancers such ovarian and endometriosis, heart conditions, and autoimmune illnesses were risk factors for pcos. Pregnancy-related issues in PCOS patients include miscarriage, preeclampsia, ectopic pregnancy, and preterm delivery. PCOS is associated with some psychiatric issues, including insomnia, eating disorders, depression, anxiety, social phobia, personality disorders, and attention deficit hyperactivity disorders. PCOS cannot be cured, but it can be controlled with medication and lifestyle changes. Metformin, clomiphene, letrozole, orlistat, isotretinoin, inositol, statins, oral contraceptive pill, spironolactone, folic acid, flutamide, vitamin E, vitamin D are the drugs that are usrd in the treatment if pcos. Surgical approaches such as ovarian drilling, IVF, bariatric surgergy are done in pcos treatment. PCOS treatment involves surgical methods such as ovarian drilling, IVF, and bariatric surgery. In patients with pcos, other methods such as laser therapy are used to remove unwanted hair. A calorie deficit, regular exercise, and avoiding a sedentary lifestyle are all lifestyle changes that can greatly aid in the management of PCOS.

Chapter four
Methodology

A review on Polycystic Ovary Syndrome (PCOS) Epidemiology, Symptoms, Diagnosis, Risk Factors & Treatment

4.1 Introduction

The examination is preceded with a literature review. For this work, a number of research papers and websites are reviewed.

4.2 Research Design

Google Scholar, PubMed, and other websites were used to design the research to find relevant literature for this research article.

4.3 Search Strategy

The following keywords can be used to search for information: polycystic ovary syndrome, rotterdam criteria for pcos, prevalence, epidemiology of pcos, risk factors of pcos, diagnosis, etiology, medications used in pcos, lifestyle modification of pcos, and surgical treatment for pcos. Additionally, reference lists for the sources were scanned.

Chapter five
Result & Discussion

5.1 Result& Discussion

A complex endocrine condition that affects women at all stages of life is polycystic ovarian syndrome. Menstrual abnormalities, acne, hirsutism, and obesity are common in adolescent females, which can further contribute to body image issues, low self-esteem, anxiety, and depression in them. Women with PCOS may have trouble getting pregnant on their own and may require reproductive therapy. Additionally, these women are susceptible to recurrent miscarriages. They are more likely to develop diabetes, hypertension, and cardiovascular diseases later in life. They run the risk of developing endometrial hyperplasia and endometrial cancer due to the unopposed estrogen. Measures used as part of management frequently aim to lessen symptoms or stop consequences linked to the illness. Although there is no treatment for PCOS permanently, lifestyle changes such as weight loss, exercise, meditation, and a good diet are seen to assist PCOS women manage their symptoms. Therefore, it is crucial to raise community awareness of the risk factors, symptoms, and complications as well as when and where to get treatment. Along with this, it's crucial to emphasize the significance of adopting a healthy lifestyle in today's society, when stress, sedentary behavior, and preserved food are the new normal. (Dr.Asmita Kaundal, February 25th, 2022).

Chapter six
Conclusion

6.1 Conclusion

PCOS is a disease whose prevalence is dramatically rising. Additionally, this disease has connections to other diseases. PCOS cannot be cured; rather the disease can be managed by a mix of therapy and lifestyle changes. The treatment and management of PCOS are considerably aided by early detection and not ignoring the signs of PCOS.

Chapter seven
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7.1 Reference

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