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The Clinical Manifestations of Polycystic Ovary Syndrome (PCOS) and The Treatment Options

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ABSTRACT: *Polycystic Ovary Syndrome is one of the most common endocrine disorders in females. It is important to diagnose early using the correct diagnostic criteria to ensure proper management and to reduce the long-term effects.To aggregate data on females diagnosed with PCOS and study the prevalence, symptoms, diagnostic criteria, and treatment options available till date for this syndrome.**A** thorough literature search of PubMed, Medline, and Google Scholar for data sources mentioning the symptoms and diagnostic criteria for PCOS in females to date is included in the study. A total of 61 articles were used and a total of 10 were excluded due to repetition of data or studies with sample sizes less than 70.Women clinically diagnosed with PCOS. The prevalence of PCOS was more common in woman aged 21-34 years and varied from 2.2% to 20% in different parts of the world. The most common symptoms found for PCOS were menstrual irregularities, hirsutism, weight gain, and insulin resistance. There are 3 diagnostic criteria currently being used to diagnose PCOS namely Ovulatory Dysfunction, Hyperandrogenism, and Polycystic Ovarian . The symptoms of PCOS vary greatly among women and so treatment is largely based on the presentation of symptoms and prevention of long-term effect. Therefore, the main treatment options for menstrual irregularities areClomiphene Citrate, Letrozole, Oral Contraceptive Pills (OCPs) a second-line therapy includes Gonadotropins, Metformin and Laparoscopic Ovarian Drilling (LOD). Hyperandrogenism treatment options are Finasteride, Isotretinoin, Spironolactone and Flutamide. Simultaneously weight reduction therapy, lifestyle changes can be used to reduce a weight gain.The prevalence of PCOS is influenced the diagnostic criteria used. The Clinical presentations of PCOS vary greatly among women. Rotterdam criteria, most widely used to diagnose PCOS, include the presence of at least two of these three conditions: polycystic ovaries on ultrasound imagining; hyperandrogenism; and chronic ovulatory dysfunction. The treatment of PCOS is not specific. Lifestyle modifications, pharmacotherapy and some surgical approaches have been successfully used to manage the symptoms.*

KEYWORDS: clinical manifestations, polycystic ovary syndrome (PCOS) treatment, options

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INTRODUCTION

Polycystic Ovary Syndrome is a multifactorial disorder that most times is diagnosed via a process of eliminating other disorders. It affects multiple aspects of a women's overall health. The prevalence of PCOS varies depending on the diagnostic criteria which are used, and the treatments of PCOS are based on the clinical presentations (Deswal.R.et.al.2020). In 1935, Stein and Leventhal published the earliest complete description of the polycystic ovarian syndrome (PCOS) (Stein & Leventhal, 1935). This had sparked much research controversy because of its diverse clinical presentations, uncertain genesis, complicated pathophysiology, and poor diagnostics (Hollinrake et al., 2007; Huang et al., 2010). In therapeutic endocrinology, the diagnosis of PCOS is still up for debate. The National Institutes of Health (NIH) criteria were established in 1990 to produce a comprehensive and detailed standard for the diagnosis of PCOS (Frank. S, 1995). Later in 2003, a meeting in Rotterdam developed the Rotterdam criteria, a diagnostic parameter which needs the existence of two of these three conditions: oligomenorrhea/anovulation, hyperandrogenism, and polycystic ovaries. (Azziz et al., 2006).

The incidence of PCOS is influenced by several genes and environmental variables. A study looked at the etiology of PCOS found genes engaged in gonadotropin and neuroendocrine action, ovarian androgen production, and probable insulin action, which provided insight into PCOS' historical route (Azziz, 2016). The symptoms tend to vary widely and include infertility, menstrual irregularities, obesity, insulin resistance, hyperandrogenism such as hirsutism, acne, and alopecia, and the appearance of multiple cysts on the ovaries visible on ultrasounds. PCOS is also associated with an increased risk of type 2 diabetes and endometrial cancer. (Azziz, 2016).

Insulin resistance is thought to be the primary cause of hyperandrogenism and associated clinical features of PCOS, affecting between half to seventy percent of individuals (Stepto, N.K., et al., 2013). Metformin, an insulin sensitizer, was reported to reduce menstrual irregularities and ovulation incidence in women having PCOS, with the effects assumed to be achieved by enhanced insulin tolerance and reduced androgen synthesis (Pasquali, 2014).

PCOS is a hormonal disorder that has reproductive, metabolic, and psychosocial consequences. The disorder's severity and impact on quality of life necessitate prompt diagnosis, screenings for consequences, and management measures. However, PCOS is difficult to diagnose as not all women present with the same combination of symptoms and therefore it is still under-diagnosed. As there is no sole treatment option for PCOS, the treatment is based on the presenting symptoms. As a result, effective distribution of evidence-based administration is critical.

Purpose of the Study:
The purpose of this study was to systematically review the literature and provide an overview of

prevalence, clinical presentation of PCOS along with its diagnostic criteria and therapeutic choices. Prevalence study will be helpful to inform researchers, guideline developers and policymakers about burden of disease, thereby supporting the process of identification of priorities in healthcare, prevention and policy. Highlighting the symptoms and diagnostic criteria will assist in the easy identification and diagnosis of the PCOS. The treatment options discussed in this study will aid managing the symptoms and improving the quality of life of the patient.

METHODS AND MATERIALS

A thorough literature searches of Pub Med, Medline, and Google Scholar for data sources mentioning the Symptoms and diagnostic criteria for PCOS in females to date is included in the study. The effects of polycystic ovary syndrome were investigated through these sources.The key words used to search the appropriate articles were "PCOS", "infertility"," "oligomenorrhea" or "amenorrhea", "obesity", "insulin resistance" and "hyperandrogenism".Descriptive data of each symptom and the treatment options were compiled from published data of sample sizes greater than 70.

LITERATURE REVIEW

Prevalence

Polycystic Ovarian Syndrome (PCOS) is a very prevalent disorder and affects females in various ways. The prevalence of PCOS is greatly determined by the guidelines used. New guidelines for diagnosing and treating PCOS were announced in November 2015 by the American Association of Clinical Endocrinologists (AACE), American College of Endocrinology (ACE), and Androgen Excess and PCOS Society (AES). (Goodman et al., 2015). Two out of these three conditions should be present to diagnose PCOS: persistent anovulation, hyperandrogenism, and polycystic ovaries along with the identification of the phenotype.

In a study conducted by Yildiz et.al (2021) in December 2009 in a group of 392 women ages 18-45 years of the same population, the prevalence of PCOS using the National Institutes of Health NIH criteria was 6.1%, the prevalence of PCOS using the Androgen Excess and Polycystic Ovary Syndrome Society (AE-PCOS) criteria was 15.3%, while the prevalence of PCOS using the Rotterdam criteria was 19.9% (Yildiz et. al 2021).

The prevalence of PCOS among different geographic regions estimated from five studies conducted between 2010 to 2014 on study groups greater than 447 females found ranges from 5%-10% using the NIH criteria, 6%-21% using the Rotterdam criteria, and 10%-15% using the AE-PCOS criteria. The difference in estimates of PCOS prevalence in the Rotterdam, NIH, and AE-PCOS criteria is largely due to the inclusion of additional phenotypes in the criteria. The Rotterdam criteria are inclusive of more symptoms and therefore the prevalence rates are higher. (Lizneva D et.al 2016).

According to studies conducted between 2006-2014 using the Rotterdam criteria on sample sizes greater than 1000; Iran, China, and the U.S.A reported a prevalence of 3%, 2.2%, and 4.7% respectively. Brazil, Beijing, Sri Lanka, Palestine, Greece, the UK, and Spain reported prevalence rates of 5%-10%. Denmark, Turkey, and Australia reported rates of 15%-20%.

In a study conducted by Dayo et.al in 2016 using various diagnostic criteria to determine the prevalence of PCOS according to race and ethnicity in 405, 580 women in California, ages 21- 44 years from 2015 to 2016. It was found that the prevalence among whites were 1.3% - 1.6%, Hispanics 1.4% - 2.4%, Blacks 1.2% - 2.5%, Chinese 0.8%- 1.9%, Filipino 1.4% - 2.1% and South Asians 2.0% - 3.5%. From the sample, PCOS was more prevalent among women 21-34 years than women aged 35-44 years.

Symptoms of PCOS

The Clinical presentations of PCOS vary greatly among women. PCOS may present as ovarian dysfunction and menstrual irregularities, obesity along with signs of androgen excess such as hirsutism, acne and alopecia, and polycystic ovaries on imagining in females. PCOS is a common cause of infertility and puts females at risk of developing type 2 diabetes, and endometrial cancer. (Balen.A.H.2017).

In a study conducted by Chaudhari et.al on 70 women aged 18-45 years diagnosed with PCOS via the Rotterdam criteria the prevalence of various symptoms of PCOS were Alopecia 32.9%, Hirsutism 37.1%, Acne 55.7%, Obesity 58.6%, and Menstrual Irregularities 95.7%.According to a study, around 30% of the 1871 women having polycystic ovaries on ultrasound and at least one other sign of PCOS possessed a regular monthly cycle, 50 % had oligomenorrhoea, while 20% as amenorrhoeic (Balen et al., 1995). According to one study, PCOS affects 80 - 90 % of females with oligomenorrhoea and up to 30–40% of females with amenorrhea (Goldzieher & Green, 1962).

Infertility

Infertility is prevalent in 70% - 80% of females with PCOS and should be evaluated after one year of having frequent unprotected sex. It increases with women's age, lifestyle factors such as smoking, illicit drug use, alcohol, caffeine, and environmental factors such as pollution, exposure to heavy metals, toxic chemicals and radiation (Sharma.R. et.al. 2013). Single gene disorders leading to infertility have also been identified but only contributed to a small percentage of infertilities. The most common type identified is the single –nucleotide polymorphism (SNPs). Defects in the LHCGR gene which encodes the luteinizing hormone (LH), and human chorionic gonadotropin receptors can also affect the normal menstrual cycle. (Pisarska.M.D. et.al. 2019).

Exposure to androgen excess due to PCOS can disrupt the normal LH: FSH ratio which in turn disrupts follicle growth, maturation and regular release of the egg inhibiting ovulation and resulting in infertility. However, the mechanism by which ovarian dysfunction occurs is still unclear (Qu. F et.al 2012). Ovarian dysfunction presents as irregular menstrual cycles. If ovulation

does not occur, the endometrium becomes thick and does not shed and regrow as in a normal menstrual cycle. The thickened endometrium may shed irregularly causing heavy or prolonged bleeding. Women with PCOS may have less than six to eight menstrual periods per year. Endometrial thicken caused by absent or irregular periods increase the risk of developing endometrial hyperplasia and endometrial cancer (Barbieri. R et.al. 2013).

Hyperinsulinemia promotes the biosynthesis of androgens from the ovaries and adrenal glands resulting in hyperandrogenism. Excess androgens convert to estrogen which increases LH secretion from the pituitary. Insulin also acts on granulosa cells of the small follicles and amplifies premature responsiveness to LH. This leads to premature differentiation and arrest of the follicular growth and results on anovulation (Sakumoto. T et.al 2010).

Obesity

PCOS affects a substantial percentage of women who are obese. Obesity can exacerbate the other symptoms of PCOS and PCOS can also lead to weight gain and obesity. Obesity is prevalent in 35% - 60% of women diagnosed with PCOS (Vribikova. J et.al. 2009). Other studies show that 35–50 percent of PCOS women were obese (Kiddy et al., 1990; Gambineri et al., 2002).

The obesity rate in women having PCOS had risen from 51 percent in 1987–1990 to 74 percent in 2000–2002, as per a US survey (Yildiz et al., 2008). In contrast, an Italian analysis revealed that just a 14 percent of women with PCOS reported being obese (Targher et al., 2009). Hyperandrogenism, irregular menstrual cycles, sterility, insulin resistance, and dyslipidemia are all worsened by excessive bodily weight (Balen et al., 1995; Holte et al., 1994; Brassard et al., 2008; Kaya et al., 2009). In women experiencing PCOS, obesity raises their incidence of metabolic syndrome, impaired glucose tolerance (IGT), and type 2 diabetes (Moran et al., 2010).

An increase in adipose tissue also leads to greater metabolism of cortisol which results in the activation hypothalamic-pituitary-adrenal axis which leads to an increase in the production of dehydroepiandrosterone (DHEA) synthesis which in turn leads to the production of androgens and estrogen. High adipocyte tissue also leads action of aromatase, which increases extra ovarian estrogen synthesis. (Rojas J et.al. 2014) Obesity increases the risk of developing ovarian dysfunction, miscarriage, complications in pregnancy, diabetes, and cardiovascular dysfunction (Barber TM 2019). Obesity can also favor resistance to PCOS treatments and have a negative effect on self-image, self-esteem, and quality of life. Stigma and discrimination attached to obesity along with the pressure to lose weight and maintain weight loss can pose a psychological burden. (Sarwer D.B et.al. 2016)

Hirsutism

The prevalence of hirsutism in PCOS ranges from 70% - 80% (Spritzer.P.M.et.al.2016). Hirsutism in women refers to the development of distal hair in a masculine pattern in adulthood. Excessive facial hair, hair on the chest in between breasts, or hair upon the lower abdominal area are all

typical symptoms. Family structure and ethnicity influence hirsutism. The prevalence of PCOS had been as higher as 70% in women with the condition (Hoeger, 2001).

Hirsutism can be treated with Oral Contraceptive Pills (OCP). The estrogen component in OCP acts by decreasing the amount of circulating testosterone and the progestin component acts by suppressing LH production. Hirsutism can also be treated using Spironolactone, an aldosterone antagonist, that can also function as a weak androgen receptor antagonist as well as reduce the activity of 5-alpha reductase, blocking the conversion of testosterone to the more potent androgen, dihydrotestosterone (DHT) (Pasquali. R et.al. 2014). Hirsutism may also be treated using creams, shaving, waxing, plucking, electrolysis, and laser therapy. Due to the hair cycle, most treatments require six months for results.

Diabetic Symptoms

Diabetic symptoms can include fatigue, frequent urination, increases hunger or thirst, tingling sensations in the hands and feet, and darkening of the skin in the groin, armpit and behind the neck. The signs and symptoms may go unnoticed in early stages. (Ramachandran. A et.al.2014). PCOS has been associated with and increased risk of dysglycemia independent of obesity and screening and management is highly recommended (A.E. Joham et.al. 2007).

An increase in androgens stimulates the production of insulin. Increase insulin production leads in increase in insulin resistance and hyperinsulinemia. Increased Insulin causes decreased production of sex hormone-binding globulin in the liver which leads to an increase circulating testosterone. The theca cells of the ovary are stimulated to produce androgens. Insulin increase also results in decreased release of FSH and increased LH from the pituitary. Insulin resistance and hyperinsulinemia generate inflammation which causes weight gain and is associated with an increase in the risk of type 2 diabetes and cardiovascular disease.

Aside from oligo-anovulation (Hull, 1987), women with PCOS may have hyperandrogenism (Azziz et al., 2006), polycystic ovarian morphology, elevated concentrations of luteinizing hormone, and insulin resistance and compensatory hyperinsulinism, all of which are frequently linked to obesity (Diamanti-Kandarakis, 2006). Insulin resistance is observed in 50–70% of women with PCOS (Legro et al., 2004). Metformin is widely used as it increases the peripheral uptake of glucose and increases insulin sensitivity thereby decreasing insulin concentrations. (Nestler J.E 2008).

Criteria for Diagnosis

PCOS can be diagnosed based on three sets of criteria as seen in figure 1. In 1990, The National Institute of Health (NIH) diagnosed PCOS based on the criteria of hyperandrogenism, oligomenorrhea, or amenorrhea in the absence of all other endocrinopathies. (Wang.R. et.al. 2017). The following endocrinopathies must be ruled out prior to making a diagnosis. (i) Hyperprolactinemia (ii) Congenital adrenal hyperplasia (iii) Cushing's syndrome (iv) Androgen–

secreting neoplasm (v) Acromegaly. (Chaudhari A.P. et.al.2018). In 2003, the European Society for Human Reproduction and Embryology (ESHRE) and the American Society for Reproductive Medicine (ASRM) developed what is referred to as the Rotterdam criteria which include the presence of polycystic ovaries on ultrasound imagining, and hyperandrogenism and chronic ovulatory dysfunction. Females who presented with two of these three criteria were diagnosed with PCOS with the Rotterdam Criteria. This criterion substantially increased the number of women diagnosed with PCOS as compared to that of the NIH criterion. (Carmina E.2004.) In 2006, The Androgen Excess Society defined its criteria as Hyperandrogenism and either polycystic ovarian morphology or ovarian dysfunction. Ovarian dysfunction includes irregular or absent ovulation, menses is usually irregular or absent. According to this criteria woman with anovulation with polycystic ovarian but without Hyperandrogenism were not diagnosed as having PCOS. (Azziz.R et.al.2006).

Due to controversies among the diagnostic criteria, in 2012, The NIH consensus (NIH and ESHRE/ASRM) recommended and expansion of the Rotterdam 2003 criteria to include the identification of phenotypes for PCOS (Gainder. S. et.al.2019).

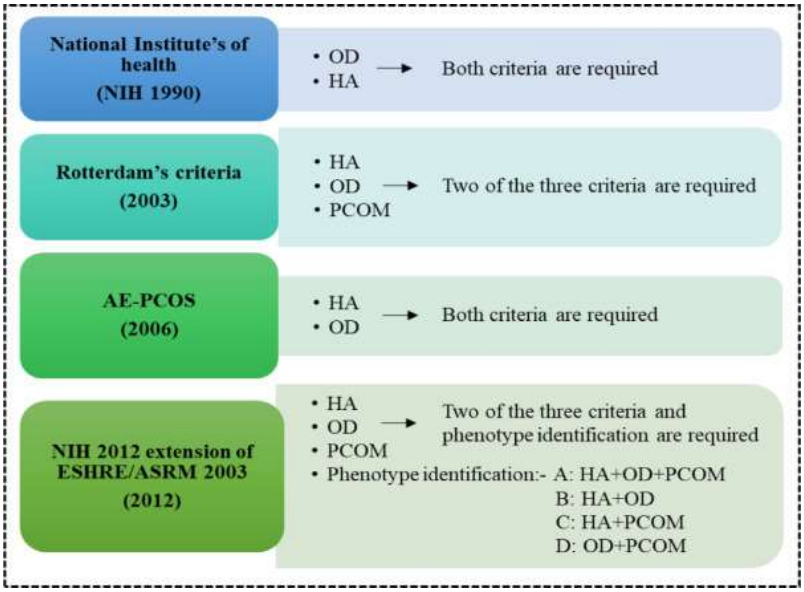

Figure 1. The Diagnostic criteria for PCOS Summary
HA = Hyperandrogenism; OD = Ovulatory Dysfunction; PCOM = Polycystic Ovarian Morphology; ESHRE= European Society for Human Reproduction and Embryology; ASRM= American Society for Reproductive Medicine.

Diagnostic Criteria for Adolescence:

Menstrual irregularities are often the earliest clinical manifestation. However, since the hypothalamic-pituitary-ovarian axis takes several years after menarche to mature this makes it difficult to distinguish the menstrual pattern and anovulation associated with puberty. Anovulation is described as consecutive menstrual intervals > 90 days even in the first year after menstrual

onset; menstrual intervals persistently <21 or > 45 days, 2 or more years after menarche; and lack of menses by 15 years or 2- 3 years after breast budding. (Kamboj.M.K.2017).

Mild hirsutism and acne are considered normal in adolescence, however, moderate to severe acne which does not respond to topical medication is evidence of hyperandrogenism. High serum testosterone levels are reliable indicators of hyperandrogenism in adolescence. (Roe.A.H et.al.2011).

Although Polycystic ovarian morphology is included in the criteria, more emphasis is placed on ovulatory dysfunction and androgen excess as ovarian appearance and volume change over time in adolescence. Polycystic ovarian morphology can be seen frequently in adolescence in the absence of metabolic abnormalities, hyperandrogenism, and anovulation and therefore cannot be used solely to assess PCOS in adolescence. PCOS can be diagnosed if anovulation persists in conjunction with androgen excess. (Codner.E. et.al.2021).

Phenotype Classification

Investigations undertaken in a Europe (Cupisti et al., 2011), the Mid East (Ramezani Tehrani et al., 2014), Asia (Li et al., 2013), the America (Melo et al., 2011), and Australia have all documented on the prevalence and severity linked to distinct PCOS phenotypes (March et al., 2009).

PCOS can be classified based on four Phenotypes as seen in figure 2.

Phenotype A (Classic PCOS) presents with numerous polycystic ovaries on ultrasound, hyperandrogenism, and anovulation.

Phenotype B (Classic PCOS) presents with normal ovaries on ultrasound, anovulation, and hyperandrogenism. Phenotypes A and B are more prone to menstrual dysfunction, insulin resistance, obesity, increased risk for hepatic steatosis, and increased levels of anti-mullerian hormone (Lizneva.D. et.al.2016).

Phenotype C (Ovulatory PCOS) presents with polycystic ovaries on ultrasound and hyperandrogenism. Phenotype C has regular menstruation and symptoms appear milder than the Classical PCOS.

Phenotype D (Non-hyperandrogenic PCOS) presents with polycystic ovaries on ultrasound and anovulation without hyperandrogenism. Phenotype D is less likely to be obese and shows increased levels of LH and the LH/ FSH ratio is similar to that of the Classic PCOS. (Guastella.E. et.al.2010).

PHENOTYPE CLASSIFICATION	
Phenotype	**Features**
Phenotype A	HA + OD + PCOM
Phenotype B	HA + OD
Phenotype C	HA + PCOM
Phenotype D	OD + PCOM

Figure 2. PCOS Phenotypes and features
HA = Hyperandrogenism; OD = Ovulatory Dysfunction; PCOM = Polycystic Ovarian Morphology.

PCOS and its impact on mental health.

A study conducted by Chaudhari et.al on 70 women in the reproductive age group (18 – 45 years) who had been diagnosed with PCOS as per the Rotterdam Criteria, found the prevalence of anxiety to be 38.6 % and depression at 25.5%. They were all previously interviewed for preexisting psychiatric disorders and chosen from varying socio-economic backgrounds. Of the 70 females, it was found that 10 females suffered from both anxiety and depression, 6 had depressive episodes, 4 social phobias, 3 generalized anxiety disorders, 3 panic disorders, and 2 dysthymias. The severity of the anxiety based on the Hamilton rating scale was 62.90% mild, 29.60% moderate, and 7.40% severe. The severity of depressive symptoms was 50% mild, 38.8% moderate, and 11.10% severe. (Chadhari.A.P et.al.2018).

In an Australian study conducted by Damone et.al comparing 478 women diagnosed with PCOS and 8134 without PCOS, it was reported that the rate of depression and anxiety in women diagnosed with PCOS were 27.3% and 50% respectively as compared to 18.8% and 39.2% in women without PCOS showing that women diagnosed with PCOS are far more likely to suffer from anxiety and depression. (Damone A.L. et.al. 2019).

Hollinrake et.al conducted a study with 206 women between the age of 18- 50 seen at the University of Iowa Hospitals and Clinics. A sample comprised of 103 women who were diagnosed with PCOS as per the Rotterdam Criteria and 103 without PCOS, were chosen to access the overall risk for depressive disorders as defined by the Diagnostic and Statistical Manual IV (DSM IV). 21% of women diagnosed with PCOS experienced depressive disorders as compared to 3% from the group not diagnosed with PCOS. Depressive symptoms included fatigue, sleep disturbance, diminished interest, appetite changes, difficulty concentrating, and suicidal thoughts. Further examination was done to access the role of obesity, androgens, and other biochemical markers to determine the risk of developing depressive disorders. It was discovered that Obese PCOS woman had a higher risk (44%) of depressive disorder than the obese control (7%). The androgen levels

and lipid profiles where similar in both depressed and non-depressed PCOS subjects. The insulin levels were >100mg/dL and <125 mg/dL in non-depressed PCOS subjects compared with insulin levels > 126 mg/dL in the depressed PCOS group (Hollinrake E. et.al. 2007).

Infertility is a common presentation in patients with PCOS and is prevalent in 70-80 % of women diagnosed with PCOS. For many the ability to reproduce gives a sense of accomplishment and pride, thus the struggle to conceive can result in a tremendous amount of emotional turmoil, profound frustration, and disappointment. Infertility management can be costly and time-consuming, and many require multiple treatments and repeat trials. Infertility treatment may include lifestyle changes, drugs, Laparoscopic ovarian drilling, and in vitro fertilization. (Melo.A.S. et.al.2015).

Another presentation of PCOS which can also be linked to depressive symptoms is obesity. Although obesity is a feature of PCOS, not all women diagnosed with PCOS are obese or overweight. The prevalence of obesity in women diagnosed with PCOS is between 35% and -60 % (Vribikova.J.et.al.1990). Obesity also aggravates the reproductive and metabolic features of PCOS, and weight loss can significantly improve these features. (Barber T.M. et.al.2019). In addition, obesity can increase the risk for the development of cardiovascular diseases such as stroke and heart attack; dyslipidemia, increase the risk of hypertension, and insulin resistance

Treatments for Polycystic Ovarian Syndrome

There is no sole treatment option for PCOS, the treatment is based on the presenting symptoms. The treatments include managing the symptoms and improving the quality of life of the patient by means of lifestyle changes, pharmacotherapy and surgical approach. The management aspect of PCOS has been discussed below under the headings of treatment for infertility, treatment for menstrual irregularities, treatment for hyperandrogenism, treatment for obesity and diabetic symptoms and treatment of associated depression in the patients.

Treatments for Infertility

Lifestyle Changes

There are several treatment options for infertility, however, one of the first steps to successful conception is lifestyle changes. Due to the correlation between obesity and PCOS, it is important to ensure that dieting and exercise are included in the treatment options. Reduction of weight significantly improves the symptoms of PCOS including fertility. Weight loss reduces hyperinsulinemia, and insulin resistance and increases insulin sensitivity. It also decreases androgen levels. Other risk factors such as smoking, and alcohol use should also be assessed and stopped (Melo.A.S. et.al.2015).

Clomiphene Citrate (CC)

Clomiphene Citrate is a selective estrogen receptor modulator that acts as both an antagonist and

agonist. It is one of the first-line treatments for the induction of ovulation. CC competes with estrogen for the receptors in the hypothalamus and the pituitary. By blocking the negative feedback mechanism of estrogen, GnRH is released which stimulates the release of FSH and LH from the pituitary. This in turn leads to the stimulation of follicles in the ovaries. The side effects of CC include flushing, visual disturbances, and abdominal discomfort. (Mbi Feh.M.K. et.al. 2021).

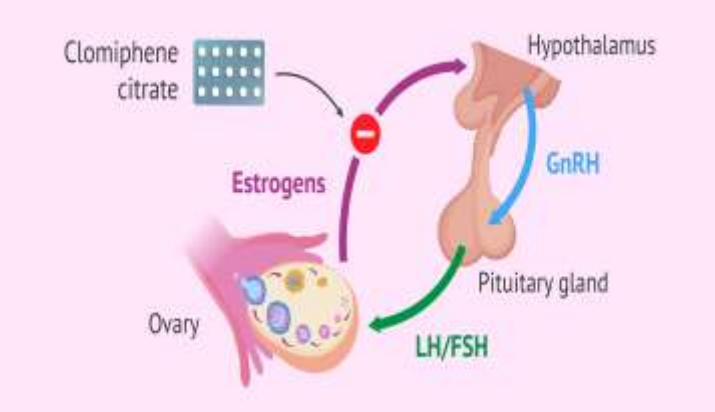

Figure 3. The Mechanism of Action of Clomiphene Citrate.
Clomiphene Citrate blocks the effect of estrogen on the hypothalamus deceasing the secretions of LH and FSH from the pituitary.

CC is low cost, can be administered orally, and has few side effects. CC can produce an ovulation rate of 73% and a pregnancy rate of 36%. Some women may not respond to CC-only therapy and may be required to use CC in combination with OCPs. The OCPs are used for 2 months to prevent ovulation by decreasing GnRH secretions, thus preventing the release of LH and FSH. The patient is subsequently treated with CC to induce ovulation. (Branigan.E.F. et.al.1999).

Letrozole

Letrozole is an aromatase inhibitor that can be used as an alternative to CC. Letrozole blocks aromatase in the granulosa cells of the ovaries thereby inhibiting the conversion of androgens to estrogen. This decreases the negative feedback mechanism of estrogen on the hypothalamus and the pituitary leading to the increased secretions of LH and FSH stimulating the release of follicles. Letrozole has an ovulation rate of 70 – 80% and a pregnancy rate of 20-27%. Side effects include GI Disturbances, hot flashes, headaches, and back pains. (Holzer.H. et.al.2006)

Gonadotropins

Gonadotropins are a second-line treatment. Recombinant follicle-stimulating hormone (rFSH) or human menopausal gonadotropin (HMG). HMG is a combination of FSH and LH. They are used for time intercourse or intrauterine insemination (IUI). IUI places the sperm directly inside the uterus, which increases the chance of pregnancy, Gonadotropins are injected under the skin and work directly on the ovary and stimulate multiple follicles. Gonadotropins have an ovulation rate of 70% and a pregnancy rate of 20%. (Thessaloniki ESHRE/ASRM -Sponsored PCOS Consensus Workshop Group (2008). Evaluation of tubal patency is suggested prior use of gonadotropins.

Gonadotropin therapy has a high cost and requires regular monitoring via ultrasound for follicular development. The side effects are abdominal discomfort, headaches, and nausea, multiple pregnancies. There is also an increased risk of the ovarian hyper-stimulation syndrome in which ovaries become enlarged due to the multiple developing follicles. The risk of multiple pregnancies is also increased. (Balen A.H. 2013).

Metformin

Metformin is a third-line treatment and acts indirectly to induce ovulation by decreasing the concentration of insulin. Treatment usually takes five weeks. It is also useful in the treatment of other PCOS symptoms. Metformin can be used as a single therapy with an ovulation rate of 34% or in combination with CC. When used in combination with CC the ovulation rates are up 90%. The side effects of Metformin include GI Disturbance and lactic acidosis. (Legro.R.S. et.al.2007).

Laparoscopic Ovarian Drilling (LOD)

Laparoscopic Ovarian Drilling (LOD) is considered a second-line therapy and is used when clomiphene citrate and other first-line therapies fail. It is a surgical procedure that requires the use of anesthesia and is a high-cost procedure. LOD involves the use of laser or electrocautery to drill four to ten holes in the thick outer surface of the stroma of the ovary. Creating these holes in the tissue, decreases the number of androgens produced and therefore less androgen is converted to estrogen. This corrects the negative feedback mechanism on the hypothalamus and pituitary allowing for the maturation of follicles. If the patient does not present with an ovulatory cycle after three months, then the procedure is combined with CC. If there is still no ovulation cycle after six months, the patient should be treated with gonadotropin therapy (Bordewijk.E.M. et.al.2020). LOD has an ovulation rate of up to 80% and a pregnancy rate of up to 60% (Amer.S.A.K. et.al. 2004). The risks associated with LOD include complications from anesthesia, damage to ovarian tissue, infection, and adhesions. (Mitra.S. et.al.2015).

Assisted Reproductive Technology (ART) – In Vitro Fertilization

Assisted reproductive technology is used in the treatment of infertility. It is a third-line treatment of infertility with PCOS but may be considered first-line for women with blocked or damaged fallopian tubes. The procedure involves stimulation of the ovaries to produce multiple follicles with gonadotropins or CC. As the follicles mature, the hormone, human chorionic gonadotropin (hCG) or Gonadotropin-releasing hormone (GnRH) antagonist is given to induce ovulation. The mature eggs are harvested from the ovaries and fertilized with healthy sperm. Once fertilization is successful, the embryo is implanted into the lining of the uterus. Estrogen and progesterone can be administered to prepare the uterus walls. The most common complication of ART is multiple pregnancies. This, however, can be minimized by limiting the number of implanted embryos. (Eskew.A.M. et.al. 2017).

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Treatment for Menstrual Irregularities

Oral Contraceptive Pills (OCPs)

Anovulation is the major cause of infertility and can lead to long-term effects such as endometrial hyperplasia and cancer. OCPs with a combination of estrogen and progestin can be used to reduce gonadotropin stimulation on the ovary and reduces androgen production. Progesterone inhibits hyperplasia of the endometrium, inhibits the secretion of LH and thickens cervical mucus. Estrogen inhibits FSH. (Badawy.A. et.al. 2011). Along with regulating the ovulatory cycle, OCPs also help with acne and hirsutism. The side effect of OCPs includes nausea, vomiting, weight gain, spotting and bleeding, breast tenderness, and decreased libido. (Cooper.D.B. et.al.2021).

Treatment of Hyperandrogenism
The most common clinical features of hyperandrogenism are hirsutism, acne, and alopecia.

Treatment of Alopecia:
Finasteride
Finasteride is a 5-alpha reductase inhibitor. 5-alpha reductase inhibitors act in the hair follicles to inhibit the conversion of testosterone to dihydrotestosterone (DHT) which is the androgen responsible for male pattern baldness. Finasteride promotes scalp hair growth and prevents further hair loss. Side effects include decreased libido, enlarged breast, tenderness, dizziness, weakness, and skin rash. (Zito.P.M. et.al. 2021).

Treatment for Acne:
Isotretinoin
OCPs are the first-line treatment for acne along with antiandrogens. However, in more severe cases of acne, Isotretinoin is the drug of choice. Isotretinoin is a form of the vitamin that is known as 13-cis-retinoic acid. Isotretinoin works by altering the cell cycle, cell differentiation, survival, and apoptosis. This action reduces sebum production, preventing blockage of pores and the growth of acne-causing bacteria. It can also reduce the formation of comedones by reducing hyper keratinization. The side effects of Isotretinoin include dry skin, conjunctivitis, dry mucous membranes, cheilitis, itching, joint and muscle pain, and mood changes in adolescence. (Layton.A.2009.)

Treatment for Hirsutism:
The growth phase of the hair cycle is approximately 4 months for facial hair, therefore hormonal treatments require at least 6 months to produce results.

Oral Contraceptive Pills (OCPs)
OCPs are the first-line treatment for several symptoms associated with PCOS including hirsutism.

The direct negative feedback on LH secretion and androgen release by the ovary is reduced. OCPs inhibit the peripheral conversion of testosterone to DHT and decreases free circulating androgens by increasing the production of the sex hormone-binding protein in the liver. (Cooper.D.B. et.al.2021). Reduction of androgens result in decreased conversion of thin vellus hair to thick terminal hair.

Metformin

Increasing insulin sensitivity, metformin can in turn reduce circulating androgens and can therefore help reduce symptoms of hyperandrogenism such as hirsutism.

Antiandrogens: Spironolactone and Flutamide

(a)Spironolactone is an aldosterone antagonist, that also functions as an androgen receptor antagonist. It also reduces the activity of 5 alpha-reductase. Spironolactone not only reduces hirsutism but also reduces insulin resistance and fasting insulin levels. Spironolactone as single therapy may cause menstrual irregularities and feminization of male fetuses; it is therefore commonly combined with OCPs. Other side effects include hyperkalemia, fatigue, and upset stomach. (Cumming.D.C.1990).

(b)Flutamide is a potent non-steroidal antiandrogen that blocks the action of testosterone by binding to the androgen receptors. It is used primarily to treat prostate cancer; however, it is used to treat hirsutism, alopecia, and acne. Due to its teratogenic effect, it is used in combination with OCPs. Other potential adverse effects include hepatotoxicity, hot flashes, decreased libido, impotence, gynecomastia, nausea, diarrhea, and vomiting. (Johnson.D.B et.al.2021).

Topical Treatments:

Eflornithine

Eflornithine is a topical treatment that irreversibly inhibits the enzyme ornithine decarboxylase in the skin. It inhibits cell division and differentiation, therefore, reducing the rate of hair growth. Eflornithine can also be used with laser treatments, OCPs, or antiandrogens. Side effects include stinging, burning sensation, and alopecia. (Shapiro.J.et.al.2005).

Direct Hair removal

Unwanted hairs can be removed directly by plucking, shaving, epilating, waxing, or laser therapy. These treatments can be painful, and time-consuming. Others can require multiple treatments and can be costly.

Treatments for Obesity and Diabetic symptoms

Lifestyle Changes

Obesity worsens the presentation of PCOS and therefore weight reduction is suggested as a first-

line treatment. This can be achieved through diet and exercise. Diets should include lean meats, high fiber, and increased water intake. Alcohol, refined sugars, processed foods, and flour-based products should be reduced. Exercises should include aerobic exercises as well as strength training. The reduction of weight by as little as 5% is shown to normalize the menstrual cycle and ovulation. (Patel.S.M. et.al.2006). It is also associated with reduced insulin resistance which leads to an improvement of metabolic functions. Weight reduction through lifestyle changes improves hyperandrogenism, lipid profiles, and fertility. It also decreases the chances of developing type 2 diabetes and cardiovascular diseases. (Lim.S.S. et.al.2019).

Metformin

Metformin is a first-line treatment for type 2 diabetes and has also shown to be beneficial in weight loss. It increases insulin sensitivity and increases the peripheral uptake of insulin. (Rena.G. et.al.2017). It also inhibits the action of glucagon and thus hepatic gluconeogenesis, lipogenesis,

Orlistat

Orlistat is a potent and irreversible inhibitor of gastric and pancreatic lipase. It is used to sustain weight loss. It inhibits the breakdown and absorption of dietary fats. It results in significant controlled weight loss. (Jayagopal.V. et.al. 2005). The side effects of Orlistat include steatorrhea and decreased absorption of fats-soluble vitamins.

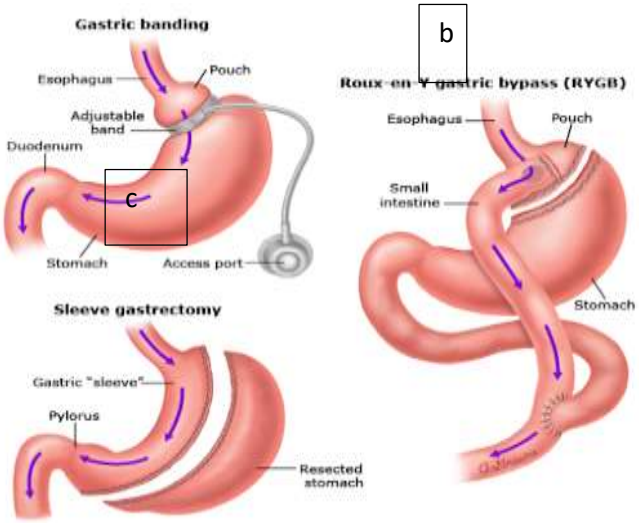
Glucagon-like peptide 1 (GLP-1) Receptor Agonist

GLP-1 Receptor agonist such as Exenatide and Liraglutide are emerging drugs for the treatment of obesity and Type 2 Diabetes. GLP-1 is a gastrointestinal hormone and is from the family of hormones known as incretins. It is produced by the cells located in the ileum and is secreted in response to nutrients in the gut. GLP-1 stimulates the secretion of insulin and inhibit glucagon secretion. GLP-1 inhibits gastrointestinal mobility and secretion and increases the feeling of fullness by acting on the appetite centers in the brain (Holst. J.J et.al. 2007).

Exenatide is an injectable GPL-1 analogue that acts on the GPL-1 receptors in the pancreas, GI tract, brain and other tissue and works to improve glycemic control while reducing body weight. Exenatide is cleared renally unlike GLP-1 which is metabolized by the enzyme DPP-4 and its half-life is prolonged in patients with kidney disease (Neff, L.M., & Kusher, R.F.2010).
Liraglutide is also an injectable GPL-1 analogue used to treat diabetes and obesity. Unlike Exenatide, the peptides have been modified to delay it absorption form subcutaneous tissue and allow reversible binding to albumin. Liraglutide has a subcutaneous half-life of 13 hours and does not undergo significant renal or hepatic clearance (Neff, L.M., & Kusher, R.F. 2010).

Bariatric Surgery

Bariatric surgery can be used in patients who cannot achieve weight loss through diet and exercise. In such cases, it offers more sustained weight loss. The most common types of bariatric surgery include:



a) Gastric band surgery: involves placing a band around the stomach. Less food is required to get a sense of fullness.
b) Gastric Bypass Surgery: this involves joining the top part of the stomach to the intestines. Less food is required to feel full and fewer calories from the food are absorbed.

Figure 4. Types of Bariatric Surgery.

c)Sleeve Gastrectomy: this involves the removal of part of the stomach so that the stomach feels full quicker.

Bariatric surgery results in significant weight loss and leads to improvements in ovulation, insulin resistance, and hyperandrogenism. (Escobar-Morreale,H.F., et.al. 2005). This type of surgery is costly and requires anesthesia and the is a risk of surgical complications. Adverse effects include Dumping syndrome in which rapid gastric emptying causes nausea and dizziness. Other side effects include malnutrition, vomiting, ulcers, bowel obstruction, and hernias. (Wolfe.B.M. et.al.2016).

Treatment for PCOS Depression

The symptoms of PCOS such as acne, alopecia, hirsutism, infertility, and weight gain can harm self-image and mental health. These PCOS presentations can lead to stress, anxiety, and depression. When treating PCOS depression, the initial course of action is to treat the underlying cause of PCOS. Therefore, treatment options such as lifestyle changes and metformin can be utilized along with the other treatment options discussed for PCOS. If the depressive symptoms persist after treating the underlying symptoms of PCOS, then an antidepressant should be considered for further treatment. (Rasgon.N. et.al. 2005).

Selective Serotonin Reuptake Inhibitors (SSRI's)

SSRI's is an antidepressant that inhibits the reuptake of serotonin in the neurons thereby increasing serotonin activity. It is used for the treatment of depression, general anxiety, panic disorder, and obsessive-compulsive disorder among other disorders. The side effects include xerostomia, GI distress, sedation, constipation, urinary retention, cognitive impairments, sexual dysfunction, and Serotonin Syndrome (Chu.A. et.al.2021). SSRIs normally take 4- 8 weeks to have an effect.

Serotonin Norepinephrine Reuptake Inhibitors (SNRI's)

SNRI's are antidepressants that inhibit the reuptake of Serotonin and Norepinephrine in the

neurons. It is used to treat depression, general anxiety disorder, and diabetic neuropathy. The side effects include nausea, dry mouth, dizziness, constipation, erectile dysfunction, and serotonin syndrome. (Lambert.O. et.al.2002).

Bupropion and Naltrexone

Bupropion is an antidepressant that acts by inhibiting norepinephrine and dopamine reuptake. It is used to treat major depressive disorder and seasonal affective disorder and aids in smoking cessation. Bupropion lacks serotonergic effects, and the side effects include sexual dysfunction, weight gain, and sedation. (Stahl.S.M et.al.2004). Naltrexone is a competitive opioid receptor antagonist which is used in combination with bupropion to counteract weight gain. The combination results in approximately 6% weight loss and has been shown to improve blood sugar levels in diabetics. The side effects of Naltrexone include dry mouth, constipation, dizziness, and nausea. (Shah.K. et.al. 2020).

RESULTS

Polycystic ovary syndrome (PCOS) is a heterogeneous disorder characterized by hyperandrogenism and chronic anovulation. Depending on diagnostic criteria, 6% to 21% of reproductive aged women are affected. (Table 1). The Rotterdam criteria is more inclusive of symptoms and therefore higher prevalence rates are seen as compared to data collected using the other diagnostic criteria.

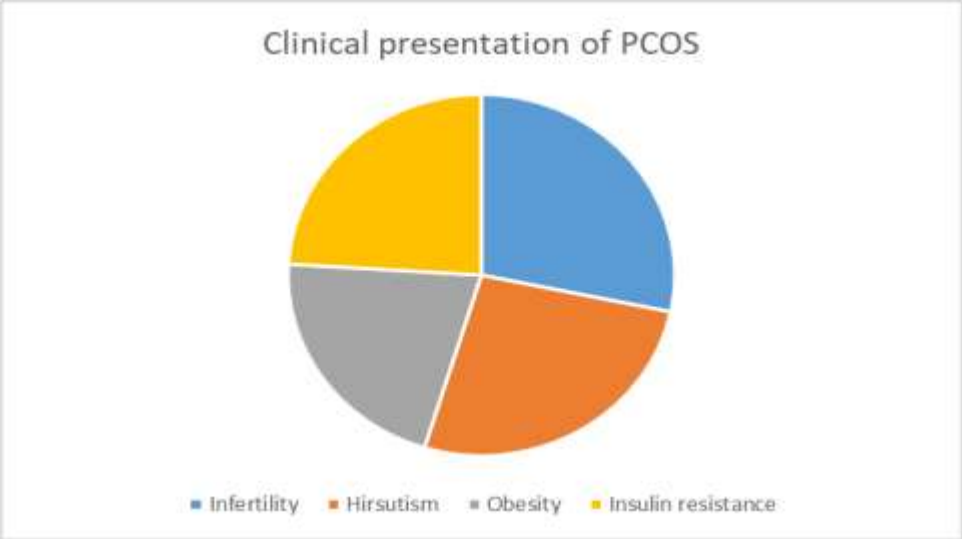
Country	Population	Number of patients	PCOS diagnostic criteria in %			Reference
			NIH 1990	Rotterdam 2003	AE-PCOS 2006	
Australia	Indigenous women in Darwin Region Urban Indigenous Diabetes (DRUID) study.	248	15.3	21.3		March W.A, 2010
Brazil	Women undergoing cervical cancer screening	859		8.5		Gabrielli L, 2012
China	Residents of Chengdu	1645	7.1	11.2	7.4	Zhang H.Y, 2014
Denmark	Employees at Copenhagen University	447		16.6	13.9	Lauritsen M.P, 2014

Greece	White women general population recruited via offer for a free medical evaluation	192	6.8			Diamanti-Kandarakis, 1999
Iran	Four random provinces of different geographic regions	929	7.1	14.6	11.7	Sirmans S.M, 2014
Mexico	Hospital employee volunteers	150	6			Moran C, 2010
Spain	Blood donors in Madrid	154	6.5			Asuncion M, 2000
Sri Lanka	Four areas in Gampaha region	2915		6.3		Kumarapel V, 2008
Turkey	Pre-employment medical assessment in General Directorate of Mineral Research and Exploration	392	6.1	19.9	15.3	Yildiz B.O, 2012
UK	Volunteers in Oxford	277	6			Knochenhauer E.S, 1998
USA	Pre-employment medical assessment in the South-eastern USA	400	6.6			Azziz R, 2004

Table 1. The prevalence of PCOS in different countries using various diagnostic criteria.

The most common clinical presentations of PCOS are Infertility due to ovarian dysfunction / menstrual irregularities, obesity, hirsutism, and insulin resistance.

Infertility is prevalent in 70%-80% of females and is a common finding in PCOS. Another equally common presentation is hirsutism which is also seen in 70%-80% of females. Obesity is prevalent in 35%-60% and insulin resistance in 50%-70% of females. (Graph 1)



Graph 1: Clinical presentation of PCOS

The symptoms of PCOS vary greatly among women and so treatment is largely based on the presentation of symptoms and prevention of long-term effects. Treatments options include lifestyle changes such as diet and exercise, and pharmaceutical drugs.

Table 2. Summary of different treatment options in management of PCOS.

Treatment options	**Symptoms**
Clomiphene Citrate	Ovulation induction
Gonadotropins, Letrozole	Ovulation induction
Spironolactone	Hirsutism, acne
Oral Contraceptives	Regulation of menstrual Cycles, Hirsutism, prevention of endrometrial cancers
Pioglitazone, Rosiglitazone	Hyperinsulinemia, androgen excess, anovulation
Myo-inositol and d-chiro-inositol	Androgen excess, anovulation
Bromocriptine	Anovulation
Metformin	Hyperinsulinemia, Androgen excess, anovulation
Sitagliptin, Alogliptin and Linagliptin	Hyperinsulinemia, obesity
Empagliflozin	Obesity, androgen excess, Hyperinsulinemia
Statins	Hyperandrogenism, Dyslipidemia
Isotretinoin, Spironolactone, Flutamide Liraglutide and Exenatide	Weight loss, anovulation, Hyperandronenism, Hyperinsulinemia
Eflornithine	Hirsutism

The administration of Clomiphene Citrate and Letrozole can induce ovulation, subsequently

Gonadotropins, Metformin and Laparoscopic Ovarian Drilling (LOD) is considered a second-line therapy which can also induce ovulation. (Table 2).

The Assisted reproductive technology is used as the third line of treatment for infertility.
Oral Contraceptive Pills (OCPs) can treat menstrual irregularities, Finasteride, Isotretinoin, Spironolactone and Flutamide can be used as preferable drugs for treating Hyperandrogenism.
Obese PCOS woman had a higher risk of depressive disorder hence Selective Serotonin Reuptake Inhibitors (SSRI's), Serotonin Norepinephrine Reuptake Inhibitors (SNRI's) are the preferable in treatment. Weight reduction along with controlled blood sugar levels significantly improve the symptoms of PCOS.

DISCUSSION

The common presenting symptoms of PCOS include menstrual irregularities and infertility, hirsutism, alopecia, acne, obesity, and insulin resistance. Women with PCOS are at increased risk for endometrial cancer, diabetes, and cardiovascular disease. The prevalence of PCOS is based on the diagnostic criteria used.
The diagnosis of PCOS can be made using three different diagnostic criteria. The NIH 1990 criteria, the Rotterdam 2003 criteria, and AE-PCOS 2006 criteria. The Rotterdam criteria are more widely used if symptoms are more expansive. The criteria include identification of hyperandrogenism, ovulatory dysfunction, and polycystic ovarian morphology on imagining. PCOS can further be classified into four phenotypes, A, B, C, and D.

The phenotypic definition of PCOS is not uniform, but rather relies on the existence or omission of three elements: hyperandrogenism, menstruation irregularities, and Polycystic Ovarian Morphology. Varied phenotypes may react in various ways to ovulation inducing drugs like clomiphene. These distinctions indicate that each PCOS phenotype is a variant of a similar condition. It is possible that genetic and environmental variables interact to influence PCOS aetiology (Franks et al., 2006).

A study found that phenotypes A, B, C, and D remained prevalent in 60.2 percent, 16.1 percent, 18.3 percent, and 5.4 percent of the population, however (Gluszak et al., 2012). Another study conducted on the Bulgarian population yielded comparable findings (Pehlivanov & Orbetzova, 2007). Furthermore, obesity, hyperandrogenism, insulin resistance, abnormal lipid profiles, and metabolic disorders were shown to be significantly prevalent in phenotype A. When contrasted to the others, phenotype A has a greater risk of poor metabolic and cardiovascular effects, (Gluszak et.al.,2012) As a result, the phenotypic classification of PCOS-related infertility patients can aid in predicting the extent of the condition and the reproductive outcomes.

Infertility in PCOS is largely due to anovulation which presents as irregular menstrual cycles in females of reproductive age. Anovulation is characterized by the arrest of antral follicles, inhibiting

them from progressing to the preovulatory stage. Serum estrogen and LH are increased which results in negative feedback and suppression of FSH which is required for normal ovulation. (Frank S.1995) Infertility in females seeking to conceive can result in anxiety, depression, and low self-esteem. It can affect the female's quality of life and relationships. (Carmina E. 2004) Insulin resistance and hyperandrogenism are common features of PCOS. The exposure of adipocytes to androgen excess and hyperinsulinemia makes adipocytes prone to hypertrophy. Hypertrophic cells are more susceptible to apoptosis, inflammation, fibrosis, and fatty acid release. Hypertrophic cells cause compression in the stromal vessels, leading to adipose tissue hypo perfusion and altering secretions of cytokines such as IL6, CRP, and TNFα which subsequently promotes the cycle of insulin resistance and androgen production. Insulin resistance also promotes the conversion of preadipocytes to adipocytes, especially in the abdominal region, promoting the development of visceral obesity. (Spritzer.P.M. et.al. 2015).

Hirsutism is the foremost indicator of hyperandrogenism. Excess LH secreted by the pituitary stimulates the theca cells of the ovary to produce androgens. Androgen excess leads to an increase in the sensitivity of pilosebaceous units and conversion of villus hair which is soft, small, and light to terminal hair, which are longer, courser, and darker and is distributed in a male pattern. The increase in androgens also leads to acne and alopecia in females. (Spritzer P.M. et.al.2016). The common areas are the upper lip, chin, around breast nipples, and chest. Although the features of androgen excess may be considered inconsequential, they can result in social embarrassment and emotional distress.

Alopecia is likely underdiagnosed in someone with PCOS (Frank.S., 1989). PCOS were found in 67% of 89 women having alopecia from mixed ethnic backgrounds in a study conducted. 21% of women with alopecia have also been hirsute, as opposed to only 4% of the control group (Cela.E. et al., 2003).

With insulin resistance, the blood glucose levels may be normal, but insulin levels remain high. Insulin resistance is a characteristic feature of PCOS and is prevalent regardless of the weight of females with PCOS. The prevalence of insulin resistance in obese PCOS is 70%- 90% and 30%-75% with lean PCOS. (Stepto N.K.et.al.2013). Regardless of the criterion used, PCOS is regarded for being primarily a hyperandrogenic condition, but metabolic measures and insulin sensitivity testing are not required. Many women having PCOS have metabolic syndrome symptoms such as insulin resistance, obesity, and dyslipidemia. Recognizing the important role of insulin resistance in the development of PCOS may assist not only with the diagnosis, but also with improved diabetes and cardiovascular risk management.

Despite the inclusion of polycystic ovarian morphology, a female can have polycystic ovaries and not be diagnosed as having PCOS. (Ehrmann.David. A.et.al.1992). The variations in the diagnostic criterion of PCOS, created difficulties in a conclusive diagnosis of PCOS by clinicians as well as researchers. As a result in 2012, it was recommended the broader Rotterdam criteria be used in

conjunction with the description of the phenotype. The criteria used for adults can also be used for adolescence, however, a few challenges may arise when using these criteria. Adolescence is seen as a period of hormonal and reproductive growth and development and as such, several features suggestive of PCOS can be viewed as common in adolescence.

Women with PCOS are under a significant amount of distress as they deal with changes in their body including hirsutism, acne, weight gain, irregular or absent periods and infertility, and other associated long-term effects. Women with PCOS are also more likely to develop anxiety and depression which are largely due to their underlying symptoms. Accepting the changes in their bodies, infertility and the associated health risk can severely affect the self-image, quality of life, and overall mental health of females with PCOS. The symptoms associated with this syndrome may lead to body dissatisfaction, depression, anxiety, and diminished sexual satisfaction and affect the overall mental health and wellness of women with PCOS (Himelein.M.J. et.al. 2006). The inability to conceive as well as the treatment process can be a stressful experience that can lead to anxiety and depressive disorders, dysfunctional relationships, and low self-image. Infertile women with PCOS are more likely to experience the stress of rejection of life without a child than other women. (Basirat.Z. et.al.2019). The stigma attached to obesity leads to a negative self-image, this, in turn, can lead to anxiety and depression. The findings of this study imply that obesity diagnosis and control are significant for PCOS management. Based on interpretative and very restricted randomized controlled trial evidence, lifestyle approaches such as eating plans, workouts, behavior modification methods for changing eating and exercise habits, or a mixture of these, are regarded as first-line therapies for PCOS women who have been overweight or obese and could well enhance fertility (Moran et al., 2011; Costello et al., 2012).

Treatment for PCOS is based on specific symptoms, which may vary between individual women, and on reducing long-term effects such as endometrial cancer and diabetes. Lifestyle change is key in the treatment of PCOS, especially in obese and overweight women. Other therapies include Metformin for the treatment of insulin resistance, hirsutism, anovulation, and obesity. OCPs can be used to restore regular menstrual cycles and reduce hyperandrogenism among other therapies. From 1967, the specific estrogen receptor modulator clomiphene citrate was already utilized as a first-line clinical ovulation-inducing drug (Pritts, 2010).

Clomiphene-resistant patients are hard to address; standard gonadotropin doses are linked to a higher rate of ovarian hyperstimulation syndrome and multiple pregnancies. Low-dose gonadotropin treatment is successful in stimulating unifollicular ovulation (Gorry et al., 2006). Letrozole was first recommended as ovulation-inducing medicines in anovulation women in 2001 (Mitwally & Casper, 2001). Although there are worries about letrozole's possible teratogenic impact in fertility problems (Biljan et al., 2005), two later studies found no elevated incidence of fetal abnormality (Forman et al., 2007).

Laparoscopic ovarian drilling (LOD) had emerged as a secure and efficient surgical treatment for CC-resistant PCOS patients from its beginning in 1984. It is just as efficient as gonadotropins in based on the clinical fertility rates and viable birth rates, with the added benefit of avoiding the hazards of ovarian hyperstimulation syndrome (OHSS) or pregnancy complications (Flyckt & Goldberg, 2011; Abu Hashim et al., 2013).

Finasteride is effective in the treatment of hirsutism throughout various investigations (Erenus et al., 1997; Falsetti et al., 1997;). Isotretinoin works by reducing sebaceous efflux, inhibiting bacterial proliferation, inhibiting cell proliferation, inducing cell death in various cell types, controlling the creation of microcomedones, reducing the forming of lesions and comedones. OCPs are most commonly used for the regulation of the menstrual cycle and reduction of hirsutism, however, it may also lower insulin sensitivities and glucose tolerances in women with PCOS, according to a comprehensive study based on partial and inconsistent data (Diamanti-Kandarakis et al., 2003). A subsequent paper from the United States recognized ultimate assisted reproductive technology effectiveness using cumulative pregnancy as well as live-birth rates, displaying that after cumulative transmission of 6 embryos, cumulative live-birth rates more than 50% could be accomplished for persons below the age of 40. (Gnoth et al., 2011).

Among women with PCOS and hirsutism, the results have demonstrated a good tendency towards utilizing spironolactone (Christy et al., 2005).
Flutamide (Flu) is a non-steroidal antiandrogen without progestogenic, glucocorticoid, androgenic, estrogenic,effect (Neri.R., et al., 1972). It is promptly converted into various plasma metabolites following oral treatment, one being 2-hydroxyFlu, which is accountable for the drug's antiandrogenic effect (Brogden & Clissold, 1989). The medication works primarily by competing with androgens for cytoplasmic or nuclear attachment to the receptor (Neri.R., et al., 1972). Flutamide works by lowering androgen production (Ayub & Levell, 1987) and boosting androgen metabolism to inert molecules (Brochu et al., 1987). In facial hirsutism, eflornithine could be used as a first-line treatment (Joyner, 2004).

In comparison to surgery and pharmaceutical alternatives, lifestyle changes may be preferred and give a cost-effective primary therapeutic plan for the treatment of obesity (Clark.A., et al., 1998). Orlistat, an FDA-approved obesity therapy, is a powerful and permanent inhibitor of gastro and pancreatic carboxylester lipase, preventing nutritional triglyceride breakdown and lowering fat uptake (Douglas.I., et al., 2015). PCOS individuals, investigations evaluating orlistat and metformin found that both were equally effective at weight loss (Kumar & Arora, 2014).

In the severely obese, bariatric surgical procedure has been shown resulting in large and long-term weight loss, and hence might be a viable therapeutic option for PCOS (Skubleny et al., 2015). Because bariatric surgery had previously been proven to be the highest effective method for controlling weight loss in morbidly obese, the transfer to its use in the treatment of PCOS appears natural (Maggard et al., 2005). In morbidly obese women, weight loss mediated by bariatric

surgery seems to have a comparable impact on PCOS via improving insulin sensitivity and lowering total androgen concentrations (Escobar-Morreale et al., 2005).

This analysis imply that the clinician must choose the first-line drug for PCOS treatment after assessing the relevant information and discussing with the patient. There is no consensus upon what agent may be utilized for initial treatment. Metformin is prioritized as a first medication because it targets the metabolic irregularities in PCOS by intervening at the root of the condition. More significantly, metformin takes longer to work and tends to suppress appetite, allowing for lifestyle modifications and weight loss prior to pregnancy. Counseling pertaining to lifestyle changes, such as obesity regulation, everyday walks, avoiding alcohol and smoking, clinical symptoms (menstrual abnormalities), especially in younger girls, and insulin resistance prior to medical treatment could generate beneficial results (Beatriz Motta, 2008) in Patients with PCOS.

CONCLUSION

Polycystic Ovarian syndrome is a common disorder among women with variable presentations. The most common findings include infertility caused by anovulation, obesity, and hirsutism. The treatment of PCOS is not specific, but instead is focused on the management of the presenting symptoms and the reduction of long-term effects.

The prevalence of PCOS was found to be as low as 2.2% in China to as high as 20% in Australia and more common in woman 21-34 years' age group. Women with PCOS present as ovarian dysfunction and menstrual irregularities, obesity along with signs of androgen excess such as hirsutism, acne and alopecia, and polycystic ovaries on imagining. Rotterdam criteria, most widely used to diagnose PCOS, include the presence of at least two of these three conditions: polycystic ovaries on ultrasound imagining; hyperandrogenism; and chronic ovulatory dysfunction. The treatment of PCOS is not specific and focused on the management of presenting symptoms and the reduction of long-term effects. Lifestyle modifications focused on eating healthy and weight reduction are helpful. Pharmacotherapy of PCOS is directed mainly towards treatment of infertility, menstrual irregularities, features of hyperandrogenism, obesity, diabetes, and associated depression in the patients. Surgical approaches have also used successfully to manage the conditions in some needful patien

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