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An Overview of Polycystic Ovarian Syndrome

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Abstract

Polycystic Ovarian Syndrome (PCOS) is a multifactorial endocrine disorder characterized by hyperandrogenism, hirsutism, irregular cycles and polycystic ovaries. Obesity and metabolic disorders are common in women with polycystic ovaries and 50-70% of them are insulin resistant. The etiology of PCOS is unclear. PCOS affects 10-15% of women and 70% of cases remain undetected due to lack of information and awareness. The diagnostic method differs from PCOS in terms of diagnostic symptoms such as hyperandrogenism or abnormal menses. PCOS treatment focuses on treating symptoms such as hirsutism, oligomenorrhoea, acne, diabetes, etc. Treatment includes lifestyle improvements, metformin interventions or combined with oral contraceptives, spironolactone or switching to adult health care.

Introduction

Polycystic Ovarian Syndrome is an endocrine and metabolic syndrome in women and is characterized by irregular cycles, hyperandrogenism, hirsutism, and polycystic ovaries. insulin resistant [1]. The vast majority of women with PCOS have altered beta-cell function that increases the risk of type 2 diabetes, independent of body mass index (BMI) and age [2]. Women with PCOS also have an increased risk of developing dyslipidemia and hypertension [3]. The etiology of PCOS is not yet clear but it is thought that many things are being done. There is a link between hyperinsulinemia and hyperandrogenemia (HA) in PCOS but how this relationship is used is unclear [4].

Most PCOS-related studies are designed to improve the management of female metabolism and to develop strategies to increase fertility [5]. However, little research has been done on the pathophysiology that includes adverse pregnancy outcomes and long-term effects in children born to mothers with PCOS. It is well known that women with Polycystic ovaries are at greater risk of developing complications such as preeclampsia, pregnancy, diabetes and premature birth [6, 7]. On the other hand, young people born to women with PCOS tend to be younger in gestational age or older gestational age [6,7]. In addition, female offspring born to women with PCOS in abnormal reproductive growth [8] and also altered adrenal function [9]. Not only daughters but also a male child born to women with PCOS exhibits other metabolic factors during the child's life [10]. The hypothalamic-pituitary-ovarian (HPO) axis of women is connected and tightly controlled in the body. The HPO axis responds to internal signals (e.g. hormonal and neuronal) and external factors (such as environmental influences, lifestyle etc.).

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Pathophysiology of PCOS

PCOS develops during the first years of adolescence in a woman's body. It includes the link between genetics and environmental factors, the element of intra ovarian, the regulation of sex hormones and hyperandrogenism. Ovarian internal factors outside the ovary such as hyperinsulinimia contribute to ovarian androgen overproduction. Distributed interactions of endocrine, paracrine and autocrine factor responsible for cord maturation can also contribute to ovary release in PCOS.

Genetic

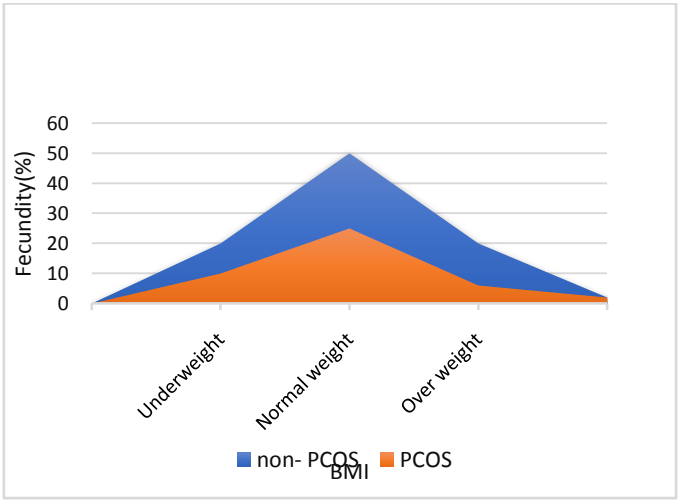
According to various studies it is evident that PCOS can be passed from one generation to the next but the reason for this is not yet clear [11]. Recently, modern mapping techniques have been used to identify PCOS passing on to the next generation.

Environmental Factor

The fetus exposed to androgens appears to contribute to PCOS. It is therefore clear that a baby born to a PCOS mother has changed the reproductive life. In the umbilical cord of women born to PCOS mothers were found to have elevated testosterone levels up to the male level [12]. Although the extent to which the mother's external environment affects the fetus is still unclear.

Obesity

Many studies had proves that weight gain contribute in the origin of PCOS[13] while weight loss can reduce the symptom of PCOS like metabolic disturbance, etc. 10-40% of PCOS patients are usually overweight (BMI> 30kg/m^2) and 40-80% are overweight (BMI> 25kg/m^2) [14].



Hypothalamus Pituitary Ovarian (HPO) axis Dysfunction

HPO is a tightly regulated system which control the reproduction in female. It generally maintain the reproductive hormone in the body like LH, FSH, GnRH etc. Large number of PCOS women have high level of LH and low or normal level of TSH. The increase in LH cause the production of androgen present in theca cells of the ovary. The theca cell layer of follicles in PCO has seen to be more thicker than in normal ovary and hypersecretion of androgen has been verified[15].Insulin also helps to increase the activation of theca cells to LH which results in the hypersecretion of androgen

and hyperinsulinemia is also common in PCOS women[16, 17]. The anti-mullerian hormone (AMH) is produced in the primary follicle and is produced by the follicle until it is selected to be dominated by FSH. After selective excretion of a prominent follicle, GCs produce inhibitors and estradiol that lower FSH levels in a negatively responsive manner [18]. The number of primary follicles is much higher in PCOS women than in normal women.

SHBG Production

SHBG is a protein stimulated by the liver. In PCOS, the level of SHBG decreases due to inhibitory effect of insulin on SHBG production [19]. SHBG helps to transfer the hormone androgen into the bloodstream as an inactive form. Reduce the level of SHBG in the body's effects on increasing biologically active androgen levels especially testosterone and 6-8% androstenedione [20].

Insulin Resistance

Insulin resistance is a condition in which the promotion of glycogen formation does not work well in major tissues in the body such as adipose tissue, liver, kidneys, skeletal muscle. In the case of insulin resistance, the insulin receptor is unable to express the adipocyte pathway and skeletal muscle [21]. Insulin resistance causes hyperinsulinimia and may also increase the level of androgen and gonadotropin through several mechanism. Ovarian stimulation is due to the combined effect of insulin on stimulating the LH of theca cells and contributes to the proliferation of theca cells [16, 17]. Insulin levels also have an effect on the level of SHBG in the body. High insulin levels reduce the rate of biologically active androgen secretion especially testosterone [19, 20].

Inflammation

Inflammation is also a key factor which contribute to the origin of PCOS. An association between increased levels of inflammatory markers (leukocyte, TNF-α, IL-6, IL-18, etc.) and the origin and development of PCOS have been observed. New problems have also included pathogenic interactions between metal saturation markers and PCOS.

Associated Disorder

PCOS women suffer from number of reproductive, metabolic and psychological complications that are associated with long term disease in PCOS women which can affect the Quality of Life of the patient.

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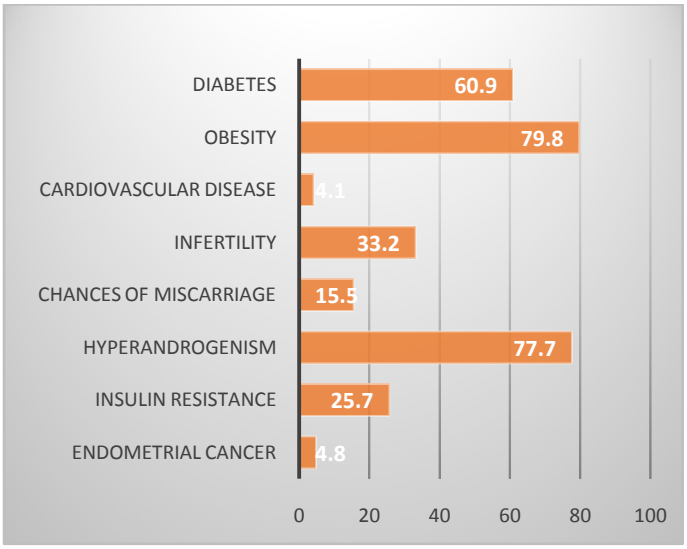

Infertility

PCOS women may have reduced fertility due to the anovulation or metabolic complication. The chances of infertility are ten times higher for PCOS women than for healthy women. First-line treatment for weight loss and administration of Clomiphene citrate. However, it can cause resistance in some women [22]. The combination of metformin and Clomiphene citrate helps maintain hormonal and metabolic actions.

Second-line Treatment involves a low dose of gonadotropin therapy containing human menopausal gonadotropin and recombinant FSH [23]. If treatment does not help the patient then in vitro fertilization (IVF) is a good option to conceive. The purpose of this procedure is to achieve ten mature follicles at the same time as menstruation.

Ovarian reserve

Ovarian reserve is the capacity of ovary to provide egg cells that are capable of fertilisation which results in health and successful pregnancy. Ovarian reserve can be measured using various measures such as FSH level, AMH level, inhibin B and no. for ultrasound detected by the antral follicle [24]. Limitation of ovarian storage helps to measure the initial dose of a particular patient. The dose of FSH and hMG is important in PCOS patients as high doses of recombinant FSH or human menopausal gonadotropin increase the risk of Ovarian Hyperstimulation Syndrome.

Pregnancy Complication

The chances of a miscarriage are much higher in women with PCOS than in normal women. PCOS women are more likely than normal women. PCOS women are generally at greater risk of pregnancy with diabetes, high blood pressure, preeclampsia and premature birth. Infants of PCOS women have increased the risk of prenatal death and are often admitted to the neonatal maternity ward [25].

Cancer and PCOS

Breast cancer, ovarian cancer and endometrial cancer are generally discussed to have association with PCOS. Endometrial cancer is thought to be caused by increased weight gain, hyperinsulinimia,

oligomenorrhoea, and increased endometrial exposure to estrogen [26]. Women with PCOS have a higher risk of endometrial cancer than women who are not PCOS as indicated by meta-analysis [27].

Metabolic Consequences of PCOS

Insulin Resistance and Type 2 Diabetes Mellitus(T2DM)

Insulin Resistance is strongly associated with PCOS and causes hyperinsulinemia.Approximately 50–70% of PCOS women suffer from insulin resistance because they have a higher risk of glucose intolerance and T2DM at an early age [2]. Numerous studies show conflicting data on insulin sensitivity in PCOS women with similar and weight controls.

Metabolic Syndrome

Metabolic Syndrome is defined as a condition in which two or more of the following symptoms are present in a person: Weight gain (obesity), decreased HDL (<1.3mmol/l, triglyceride (≥ 1.7mmol/l), high blood pressure (hypertension ≥130/≥85mmHg) and a decrease in fasting serum glucose (-6.1nmol/l) [28].In general female population metabolic syndrome is associated with increased risk of diabetes mellitus and Cardiovascular Disease(CVD)[29].

Hyperlipidemia

According to the National Cholesterol Education Program approximately 70% of women with PCOS have serum lipid levels [30] and dyslipidemia is more common in PCOS women. Thus, dyslipidemia includes high levels of LDL as well as triglycerides and reduced levels of HDL [31]. Women with PCOS increase belly fat, so they are more prone to dyslipidemia as the central adipocyte has a negative effect on blood lipid [32].

DIAGNOSIS OF PCOS

The first description of the condition of PCOS is described in mid 1930's [9]. Although a consensus definition (clinical, morphology and endocrine) which best characterised the syndrome was in 2003[33]. The range of presentation extend to find the PCO on pelvic ultrasound of women with symptoms like hyperandrogenism, menstrual irregularities and endocrine disturbances. Hyperandrogenism is considered as sensitive marker for PCOS [34].

Clinical Features

Stein and Leventhal in 1935 described seven women with PCOS had symptoms of hirsutism, obesity, infertility and enlarged Polycystic Ovaries [9]. The clinical definition of PCOS is a combination of hyperandrogenism and anointing without any adrenal or pituitary gland disease [35]. Hyperandrogenism in the female body shows hirsutism, acne and alopecia in men and the level of hirsutism can be assessed by Ferriman-Gallwey's statistics [36]. In clinical practice women are characterized primarily by three factors: A) Infertility (50-75%), B) menstrual irregularities (approximately 66%) & C) hyperandrogenism (approx. 66%) [37]. Conway analyzed 556 PCOS patients with clinical features hyperandrogenemia, amenorrhoea, infertility, polycystic ovaries in ultrasound and endocrine (increased LH) and 23 volunteers with normal ultrasound eggs with no history of hyperandrogenism and menstrual irregularities. [38]. They also found that menstrual cycle

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disorders are the most common, with about 40% of women showing irregular cycles, 26% amenorrhea and 29% infertility.

Endocrine Profile in PCOS

In the 1970s, the diagnostic process began to change to include the use of serum biochemical markers for the syndrome. Many of the endocrine parameters used in the PCOS test include increased LH circulation levels, LH/FSH ratio, testosterone, androgen-free index [18]. Women with PCOS increased Free Androgen Index and reduced Sex Hormone Binding Globulin concentration. In PCOS women there is no apparent abnormality in the pituitary, prolactin concentration is still widely distributed but serum concentrations of LH and testosterone are not related to prolactin concentration. FSH concentration is the same for healthy women and women with PCOS. Most PCOS women suffer from hyperandrogenism and circulating androgen levels may be an inherited mark of androgen excess [39]. Age and BMI were not considered when assessing androgen levels. PCOS women increased LH and FSH levels compared to normal women. Approximately 60% of PCOS women have increased LH concentration and about 95% women have elevated LH and FSH levels [40].

Ultrasound for diagnosis of PCO

Ultrasound was suggested for diagnosis in 1937. X ray pelvic pneumography is a procedure in which air is introduced into the peritoneal cavity and followed by x-ray examination was the first imaging of eggs. In the mid-1960s, ultrasonography was developed as a technical aid for the diagnosis of women by Professor Jan Donald. It allows visualization of enlarged ovaries and cysts with a diameter greater than 1cm [41]. Later, in the 1970s real-time sector scanners were developed. These devices have advanced solutions and can detect cysts in ovaries less than 1cm [42]. In 1985, Adams and colleagues studied 76 women with symptoms such as menstrual irregularities, hirsutism, acne and infertility as well as 17 healthy women with normal menstrual cycles and ovaries on trans abdominal (TA) ultrasound. They performed an ultrasound PCO diagnosis involving the presence of 2-8mm diameter cysts and their arrangement. A trans vaginal scan (TVS) was later introduced but Adams' methods are still widely used. TVS were widely used because of their high resolution. TVS have provided a more accurate view of the internal structure of the ovaries especially in obese women. TVS allow the detection of cysts less than 5mm in diameter and echogenic stroma [36].

Cardiovascular Consequences of PCOS CVD risk factor

Numerous studies have shown that PCOS women of premenopausal age have a higher risk of CVD at risk. PCOS women are thought to have a higher risk of fatal and non-lethal CVD events in the post-menstrual period. Many CVD biomarkers have been found in PCOS women at an increased cost.

In 1998, Pierpoint et al. [43] publish a registry based on long-term registry and death. Women diagnosed with PCOS in 1970 and 1979 in the UK were identified and 786 PCOS women were seen on the general medical record and in another record for 30 years. In the case of 59 deaths, the average mortality rate was the same as the national mortality rate caused by coronary heart disease or ischemic stroke [43]. The increased risk of CVD in PCOS has been widely discussed in recent years.

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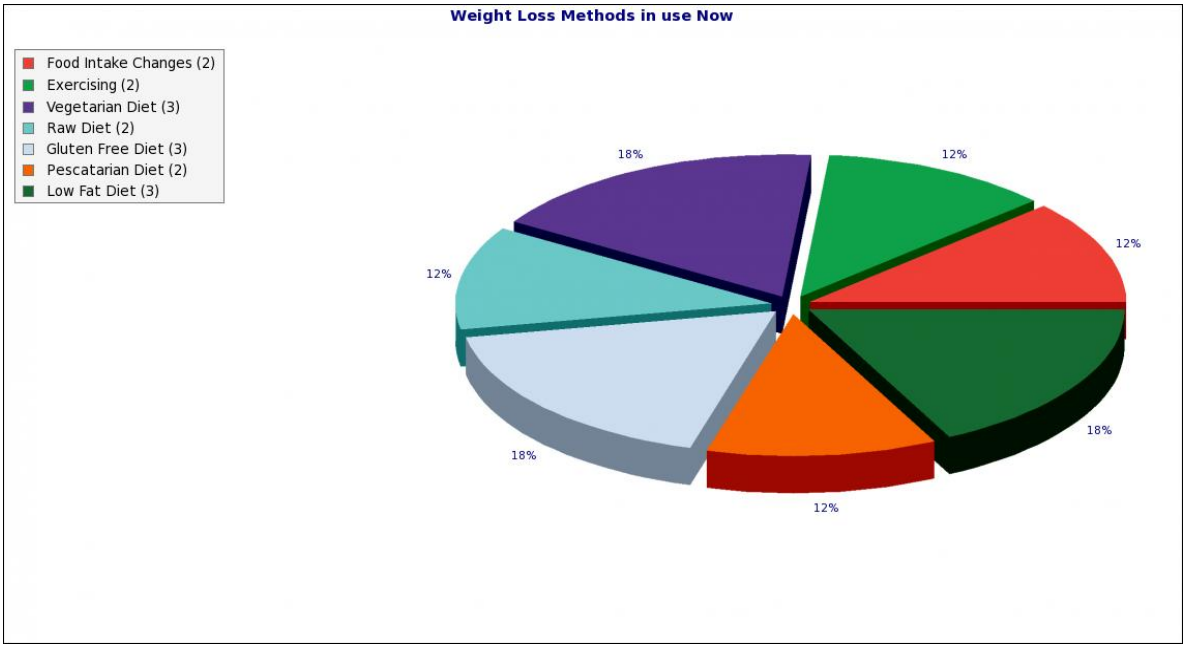
Recently the first meta-analysis on this subject was published and described for coronary heart disease / non-lethal coronary heart disease [44].

Treatment of PCOS

Lifestyle Modification

Weight management in PCOS women through lifestyle behavioural intervention which include diet & physical activity [45]. It is considered as first line treatment in PCOS. This is cost effective treatment. Weight loss controls about 5% of the menstrual cycle, improves fertility, lowers insulin and testosterone levels and contributes to mental health [46].



Pharmaceutical Treatment

Oral Contraceptive Pill

Oral Contraceptive Pills are used in the long-term treatment of PCOS women with hyperandrogenism and irregular menstrual cycles [47]. These drugs reduce LH secretion, increase SHBG and lower free testosterone levels by suppressing HPO axis. A minimum of six months oral contraceptive pills should be given to the patient to get satisfactory results. Low doses of oral contraceptive pills contain anti-androgenic or progestin neutral and may be a better choice to improve the condition [48].

Metformin

Metformin is an oral drug for biguanide. It is used as an insulin sensitizer in PCOS and shows beneficial effects on BMI and menstrual cycle. It is used as a first-line treatment for the underlying manifestations and complications of PCOS women's pregnancies.

Anti-androgen

Anti-androgen is a drug that works by blocking androgen competition that binds to the receptor or by blocking the 5-alpha reductase enzyme that lowers androgen production [49]. Active antiandrogen should be given in combination with oral contraceptives as it is more likely that a male embryo will get a woman if she becomes pregnant. Spironolactone is a very effective antiandrogen as it is effective in hirsutism, acne and alopecia. Flutamide is an inactive antiandrogen. It is very effective in combination with metformin in improving the symptoms of PCOS [49].

Education and Counselling

The education and counselling about PCOS have now become very important as many people considered it as normal condition and didn't treat it on time. But if PCOS is not treated on time it can worsen the condition and cause infertility, Diabetes or cardiovascular diseases in patient. The explanation should be culturally sensitive as well as appropriate so that person will not feel uncomfortable[50].

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