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A REVIEW ON POLYCYSTIC OVARIAN SYNDROME AND USE OF METFORMIN IN POLYCYSTIC OVARIAN SYNDROME

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ABSTRACT

Polycystic Ovarian Syndrome (PCOS) is a common reproductive-endocrine disorder in women, characterised by anovulation, infertility, and hyperandrogenism, with clinical manifestations of irregular menstrual cycles, hirsutism, and acne. Insulin resistance (IR) is believed by many to be pivotal in the pathogenesis of PCOS and that treatment strategies should revolve around reducing the IR and hyperinsulinaemia. Increased insulin levels contribute to excess androgen production and decreases hepatic SHBG synthesis results in increased circulating testosterone levels. The current therapy aims to improve insulin-resistance, which reduces compensatory hyperinsulinemia and then improve metabolic and ovulatory features in patients with PCOS. Metformin, a biguanide, is an antihyperglycemic agent decreases hepatic glucose production, decreases intestinal absorption of glucose, and improves insulin sensitivity by increasing peripheral glucose uptake and utilization. Velazquez and colleagues reported in an observational study that most of the metabolic abnormalities of PCOS can be reversed by Metformin, with the additional benefits such as allowing regular menstrual cycles, reversal of infertility, and spontaneous pregnancy.

KEYWORDS: Polycystic ovarian syndrome (PCOS), Insulin resistance(IR), Hyperinsulinemia, hyperandrogenemia, Leutinizing harmone (LH), Sex Harmone Binding Globulins (SHBG), oligo – or amennorhea, infertility, insulin sensitivity.

INTRODUCTION

Polycystic ovarian syndrome (PCOS) is the most common reproductive-endocrine disease in reproductive age women, with prevalence of 6–10% in the general population.[1]

It is characterised by anovulation, infertility, and hyperandrogenism, with clinical manifestations of irregular menstrual cycles, hirsutism, and acne. It is therefore an important health concern and may represent a major health issue affecting young women today.[2]

It was first described by Stein and Leventhal in 1935, when they noted an association between the presence of bilateral polycystic ovaries and signs of amenorrhoea, oligomenorrhoea, hirsutism, and obesity.[3]

Although the etiology of PCOS is not fully understood, evidence suggests that insulin resistance (IR), with or without compensatory hyperinsulinemia, contributes to inhibit liver sex hormone binding globulin (SHBG) production and to stimulate ovarian/adrenal androgen secretion. Environmental and genetic/epigenetic factors may also play relevant roles in PCOS development.[4] It is a common cause of menstrual irregularities and infertility during reproductive age.

PCOS can affect not only females but also males but with less frequency. Although men do not have ovaries but underlying defects (high levels of androgens and low level steroid binding globulin) and clinical features of PCOS can also be seen in males and they are referred to as SteinLeventhal syndrome.[5]

The majority of women with PCOS are overweight, adversely affecting ovarian function both directly and via exacerbation of PCOS.[6]

Women with PCOS have an increased risk of gynaecological, reproductive, medical and sleep problems, and hence are at risk of increased morbidities across the life course. PCOS is associated with an increased risk of the metabolic syndrome (11 times greater)[7] gestational diabetes mellitus (GDM) (2.4 times greater)[8] type 2 diabetes, hypertension, dyslipidemia,

subfertility, spontaneous abortions, cardiovascular events.[9]

PATHOGENISIS OF PCOS

PCOS is characterized by excessive ovarian and/or adrenal androgen secretion. Intrinsic ovarian factors such as altered steroidogenesis and factors external to the ovary such as hyperinsulinemia contribute to the excessive ovarian androgen production.[10]

Physiologically, ovarian theca cells provide support to the growing follicle, assisting in mature oocyte generation. These theca cells in PCOS patients are hyper-responsive to the stimulatory effects of insulin and cause ovarian hyperthecosis.

Insulin resistance in peripheral tissues amplifies the androgenic potential in the theca cells and further aggravates the symptoms of PCOS. Additionally, the high sensitivity of theca cells to gonadal steroid gonadotropin stimulation aids hyperandrogenism in PCOS.[11]

In PCOS, several of the physiological events within the ovarian cycle and folliculogenesis are disrupted (balance between androgens, anti-Müllerian hormone (AMH), and FSH is disrupted leading to follicular arrest. The very beginning of folliculogenesis is compromised due to high levels of Anti-Mullerian Hormone (AMH).[9]

Anti-Mullerian hormone

Anti-Mullerian hormone (AMH), a dimeric glycoprotein and a member of the transforming growth factor beta (TGF-β) family. In female, AMH is predominantly secreted by granulosa cells from preantral and small antral ovarian follicles and the absence of this hormone is responsible for the development of the female reproductive tract.It has an inhibiting effect on early follicular recruitment and thus suppresses premature depletion of follicular reserve. As the follicles grow, expression level of AMH decreased gradually. Because the production of AMH increases with the number of antral folicles**,** patients with PCOS have significantly higher serum AMH levels.[12]

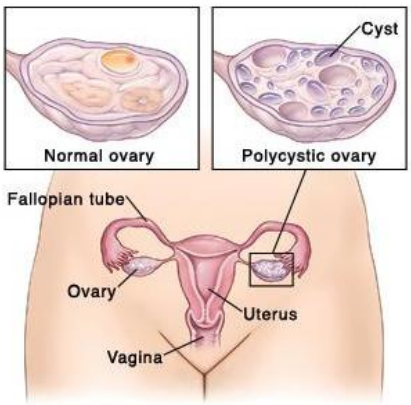

Fig. 1:

- Several theories have been proposed to explain the pathogenesis of PCOS.

1. Alteration in insulin secretion and insulin action results in Insulin resistance and Hyperinsulinemia.
2. Alteration in Gonadotropin releasing harmone results in increased leutinizing harmone secretion.
3. A defect in androgen synthesis that results in increased ovarian androgen production.

Insulin appears to disrupt all components of the hypothalamus-hypophysis-ovary axis, and ovarian tissue insulin resistance results in impaired metabolic signalling but intact mitogenic and steroidogenic activity, favouring hyperandrogenemia, which appears to be the main pathophysiologic mechanism in the development of PCOS.

INSULIN RESISTANCE / HYPERINSULINEMIA

Insulin Resistance(IR) is defined as a metabolic state characterized by a decrease in cellular ability to respond to insulin signalling, appears to be an essential pathophysiologic mechanism in the development of all metabolic complications of PCOS.[9] Insulin resistance and hyperinsulinemia are common findings in women with PCOS. Women with PCOS have a high risk of developing impaired glucose tolerance and type 2 diabetes mellitus.

The pathogenesis of Insulin resistance in PCOS reflects the interaction of genetic influences, non-heritable intra- and extrauterine environmental factors, and alternative adaptations to energy excess. Molecular mechanisms responsible for insulin resistance in PCOS include defective post-receptor insulin activity, increased free fatty acids, increased cytokine secretion, and increased androgens.[13]

Insulin which is a potent anabolic hormone controls diverse processes essential for tissue metabolism, growth, and survival. Binding of insulin to its receptor initiates a cascade of signalling events and activates an array of molecules by which insulin exerts its pleiotropic actions. The insulin receptor (INSR) is a membrane bound receptor with intrinsic tyrosine kinase activity. It is capable of binding to insulin and insulin-like growth factor-1 (IGF-1) at the alpha subunits which lead to activation of intrinsic tyrosine kinase activity and phosphorylation of the beta subunits. Phosphorylation and stimulation of these molecules play an essential role in GLUT4 translocation to the plasma membrane and glucose uptake.[14]

Elevated insulin levels, associated with insulin resistance, leads to thecal thickening in the ovary, which in turn leads to anovulation and infertility. In steroidogenic tissues such as the ovary and the adrenal cortex, insulin potentiates the cognate trophic hormones to promote steroidogenesis.[10]

The presence of IR, however, leads to a compensatory increased production of insulin by the pancreatic beta cells to control the hyperglycaemia which ultimately fails leading to T2DM. The compensatory hyperinsulinemia associated with Insulin resistance provokes excessive ovarian/adrenal androgen secretion and decreases hepatic SHBG synthesis with the net result of increasing circulating testosterone concentrations.[15]

ABNORMAL ANDROGEN SECRETION / HYPERANDROGENISM

Hyperandrogenism is defined by the state characterized or caused by the excess production of androgen or secretion of androgen, which is usually manifested by acne, hirsutism or frontal alopecia.

Androgens are part of the steroid family, mainly synthesized in ovary and adrenal gland. Cholesterol is the precursor for pregnenolone being then converted to steroid hormone after a series of enzymatic process.

In the ovary, the first step of androgen production is performed in LH-stimulated theca cells, as these cells express the cytochrome P450c17 gene. It is the key enzyme for androgen biosynthesis hence referred as 'qualitative regulator of steroidogenesis'. Thecal cells synthesize dehydroepiandrosterone (DHEA) and androstenedione. These precursors will then be converted to estrogen by granulosa cells, which express the enzyme P450 aromatase. Ovaries also directly secrete androgen in circulation, mainly androstenedione and testosterone.[16,17]

Hypothalamus secretes gonadotrophin releasing hormone (GnRH) which binds its receptors on secretory cells of adeno hypophysis. In response to GnRH, gonadotrophs produce LH and FSH, which regulate development, growth, pubertal maturation, and reproductive processesof body.[5]

The presence of dysregulated secretion of the gonadotropins, LH and FSH, which control ovarian steroidogenesis, follicular dynamics, and ovulation has been thought to play an important role in pathogenesis of PCOS. Increased circulating LH levels, increased LH:FSH ratios, elevated LH pulse frequency and/or amplitude, as well as relatively decreased FSH levels have been typically described in women with PCOS.[13]

Insulin-resistant hyperinsulinism acts on theca cells to aggravate hyperandrogenism, synergizes with androgen to prematurely luteinize granulosa cells, and stimulates adipogenesis. The increased hyperandrogenemia provokes LH excess, which then acts on both theca and luteinized granulosa cells to worsen hyperandrogenism. Testosterone is the main circulating androgen.[18]

Evidence suggests that elevated androgens disrupt the capacity of sex steroids to regulate GnRH/LH secretion via classical feedback loops. This would result in diminished negative feedback actions of ovarian steroids (estrogens and progesterone) that would contribute to and perpetuate the LH hypersecretion characteristic of PCOS.[13]

Androgens augmented by hyperinsulinaemia contribute to elevated primary and pre-antral follicles and impaired dominant follicle selection with subsequent anovulation, resulting in infertility.[6]

DECREASED SEX HARMONE BINDING GLOBULINS (SHBGS)

Sex hormone-binding globulin (SHBG), a glycated homo-dimeric plasma transport glycoprotein produced by hepatocytes, binds and controls the levels of sex-hormones within the circulation.It regulates bioavailability of testosterone in plasma via control of their respective metabolic clearance rates. SHBG concentration is a major determinant of the metabolic clearance of sex steroids and their access to target tissues. SHBG receptors (R_{SHBG}) are expressed in sex steroid-dependent cells and tissues such as ovaries, endometrium, prostate, colon, hypothalamus, breast, placenta, liver, epididymus, immune cells, and cardiomyoctes.

SHBG levels are reduced in insulin resistance and actually a good marker for insulin resistance. Abnormally low serum SHBG levels are frequently found in women with PCOS and contribute to hyperandrogenic symptoms such as hirsutism, acne, androgenic alopecia, and virilisation.[19,20]

ADIPOGENISIS / OBESITY

Obesity is present in varying degrees in women with PCOS and is associated with hyperandrogenaemia and insulin resistance.[18] Subcutaneous abdominal fat and visceral fat both contribute to the development of insulin resistance.[21] Abdominal obesity is largely prevalent in obese women with PCOS.[22]

Insulin-resistant hyperinsulinemia likely is a major factor in the excessive adipogenesis and lipogenesis of PCOS, and obesity in turn seems to aggravate the hyperandrogenism of PCOS by exaggerating insulin resistance. Proinflammatory cytokines arising from the mononuclear cells (MNCs) of adipose tissue are another mediator of the insulin resistance of PCOS.[18] The adipokine theory suggests that the adipose tissue is an endocrine organ that secretes several hormones (adipokines). Alteration in adipokines levels may lead to the development of PCOS. Adiponectin is exclusively produced by the adipose tissue.[23]

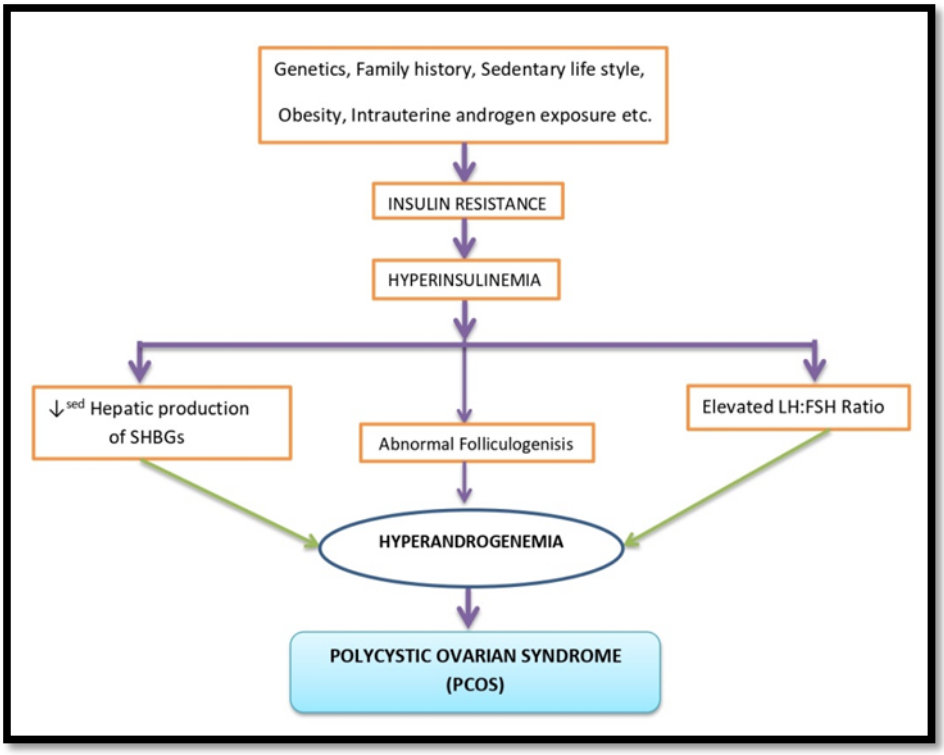

Fig. 2: Pathogenesis of Polycystic Ovarian Syndrome.

HARMONES WHICH ARE ALTERED IN PCOS

There are multiple alterations in levels of harmones in women with pcos.

- Increased levels of androgens (testosterone)
- Increased levels of Leutinizing harmone
- Decreased levels of Sex Harmone Binding Globulins (SHBG)
- Increased levels of Insulin
- Increased oestradiol and prolactin levels.[24]

SYMPTOMS OF PCOS

The symptomatic presentation of PCOS usually varies with age,young women mainly have reproductive and psychological problems while older women complaining of metabolic symptoms. Symptoms include

1. Oligomenorrhea
2. Amenorrhea
3. Hypergonadism
4. Polycystic ovaries
5. Hirsutism
6. Seborrhea
7. Acne
8. Overweight/obese
9. Alopecia
10. Infertility.[25]

CONDITIONS ASSOCIATED WITH PCOS

Women with PCOS have an increased risk of presenting with

a) Insulin resistance (IR)
b) Impaired glucose tolerance
c) Gestational and type 2 diabetes mellitus (DM2)
d) Obesity
e) Dyslipidemia,
f) Cardiovascular diseases
g) Mood disorders
h) Infertility.[26]

❖ **DIAGNOSIS OF PCOS**

Three different sets of criteria have been used for the diagnosis of PCOS for the past two decades:

1. The National Institutes of health Criteria or NIH criteria (1990)
2. The Rotterdam criteria (2003)
3. The Androgen Excess (AE) and PCOS Society (AE-PCOS) criteria (2006).

➢ **NIH-1990**

According to the NIH criteria, two conditions have to be met:

1. Chronic anovulation, documented by oligo – or amennorhea.
2. Clinical and/or biochemical signs of hyperandrogenism (Exclusion of other etiologies).

➢ **ROTTERDAM 2003**

In 2003, the Rotterdam European Society for Human Reproduction/ American Society of Reproductive Medicine (ESHRE/ASRM) proposed that the diagnosis of PCOS include any two of the following three criteria

1. Chronic anovulation, documented by oligo – or amennorhea
2. Clinical and/or biochemical signs of hyperandrogenism, and
3. Polycystic ovaries (on ultrasound); other etiologies must be excluded.

➢ **AE-PCOS SOCIETY – 2006**

The Androgen Excess PCOS Society recommends diagnosis of PCOS in the presence of hyperandrogenism plus one of two other criteria among ovulation dysfunction and PCO morphology.[27]

❖ **TREATMENT OF PCOS**

- Evidence suggests that insulin-resistance and secondary hyperinsulinemia play an important role in hyperandrogenism, anovulation or irregular cycles, and metabolic alteration in both lean and obese patients with PCOS.[28]
- Clinical management of PCOS should include rigorous lifestyle modifications, insulin therapy, and drug treatments that promote insulin sensitization (such as metformin) and insulin secretion (such as glibenclamide), dipeptidyl peptidase-4 inhibitors, sodium glucose cotransporter 2 inhibitors, and antihyperlipidemic therapy. In general, these approaches are designed to manage symptoms of insulin resistance/β-cell dysfunction and dyslipidemia and are used either alone or in combination.[29]
- Lifestyle modification is regarded as the first line treatment for women with PCOS. Exercise and weight loss improve insulin sensitivity. 44–57% of PCOS women had improvement in either menstrual cycle or ovulation after lifestyle changes and subsequent weight loss.[23]
- According to recent guidelines, insulin-sensitizer drugs are the first line therapy in women with metabolic abnormalities and irregular cycle with the purpose to improve fertility, whereas a lifestyle change with weight loss and physical activity is the first step in overweight and obese PCOS patients.[28] Treatment of PCOS with insulin-sensitizing drugs, such as metformin, troglitazone, and pioglitazone, has been shown to improve ovulatory function and reduce circulating androgens. Of these insulin-sensitizing agents, metformin is most commonly used in the treatment of PCOS.[30]
- Other treatment options include oral contraceptive pills, androgen receptor antagonists etc. Oral contraceptives improve symptoms through a variety of mechanisms. Estrogens increase the production of SHBG, resulting in a decrease of circulating free androgens, as well as their bioavailability.[31]

❖ **METFORMIN**

Metformin, a guanidine derivative that was initially extracted from the plant Galega officinalis (French lilac) has been used as a glucose-lowering medication in humans for more than 60 years. Metformin has proven to be safe and is highly cost-effective.[32]

Metformin is quite an old compound introduced into clinical use in Europe in 1957 and only in 1995 in the USA. Chemically, it is 1,1-dimethylbiguanide hydrochloride, a biguanide currently used as an oral antihyperglycemic agent for diabetes mellitus.

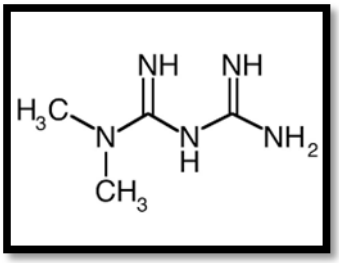

Fig. 3: Structure of Metformin.

Evidence clearly demonstrated the importance of the use of metformin, not only in the presence of diabetes mellitus Type 2, but also in patients with PCOS and hyperinsulinemia, resolving several issues such as menstrual cyclicity, fertility, hormonal levels and metabolic syndrome (MS).[33]

Its primary clinical action is to inhibit hepatic glucose production, although it also decreases intestinal glucose uptake and increases insulin sensitivity in peripheral tissues. It has also antilipolytic effects, lowering circulating free fatty acid concentrations, which ultimately aids in reducing gluconeogenesis.[34]

❖ **USE OF METFORMIN IN POLYCYSTIC OVARIAN SYNDROME**

- Insulin resistance is believed by many to be pivotal in the pathogenesis of PCOS and that treatment strategies should revolve around reducing the IR and hyperinsulinaemia.[35]
- Velazquez and colleagues reported in an observational study that most of the metabolic abnormalities of PCOS can be reversed by Metformin, with the additional benefit of normalization of endocrine abnormalities to allow regular menstrual cycles, reversal of infertility, and spontaneous pregnancy.[36]
- A magic bullet therapy for PCOS would result in weight loss, improve insulin resistance, restore normal ovulatory cycles, increase fertility, decrease hyperandrogenism, decrease the rate of spontaneous abortions, and decrease the risk of GDM. The current front runner for this magic bullet is the biguanide 'METFORMIN'.[37]
- Metformin enhances insulin sensitivity at the cellular level and also appears to have direct effects within the ovary.[38] It is commonly used in women with PCOS and is reported to improve insulin resistance, sex hormone binding globulin (SHBG), hyperandrogenaemia, and ovulation.[23]
- A dose of 1.5-2 g per day appears necessary for clinical effectiveness when metformin is used alone, the efficacy dependent on the outcome measure chosen. Arslanian reported decreased insulin sensitivity in fifteen obese adolescents with PCOS in whom metformin therapy (850 mg, twice daily) was associated with an improvement in glucose tolerance and a decrease in testosterone levels.[31]

- Metformin is available as 500, 850, and 1000-mg tablets with a target dose of 1500-2550 mg per day. Many studies in PCOS have used a dose of 850 mg twice a day for 6 months. A sustained release preparation is also available.[34]

➢ MECHANISM

- Metformin has been used for PCOS treatment since 1994, by which most of the metabolic abnormalities of PCOS can be reversed.
- The mechanism is thought to be mediated through

a) Increased insulin sensitivity
b) Increased ovarian secretion of oestrogen
c) Decreased ovarian production of androgen
d) Augmentation of the production of sex hormone binding globulin
e) Reduction in testosterone levels.[39]

➢ INCREASED INSULIN SENSTIVITY

Metformin increases insulin sensitivity by

1) Reducing gluconeogenic enzyme activities
2) Inhibiting hepatic uptake of lactate and alanine
3) Increasing the conversion of pyruvate to alanine
4) Decrease fatty acid oxidation
5) Increasing peripheral glucose uptake
6) Decreasing the glucose absorption from the gut.

➢ ANDROGEN LOWERING EFFECT

In both lean and obese women with PCOS, metformin (i) Decreases insulin levels in association with decreases in clinical indices of ovarian cytochrome P450c17 activity, and (ii) increases SHBG levels, resulting in decreases in free testosterone.[31]

- It has been suggested that metformin reduces hyperandrogenism through its effect on both the ovary and adrenal gland suppressing their androgen production, reducing pituitary luteinizing hormone and increases the production of sex hormone binding globulin by the liver.[35]
- It is well known that PCOS patients have a distinctive abnormal LH pulsatile secretion, with normal (sometimes higher) pulse frequency and higher pulse amplitude. The exaggerated GnRH induced LH response is reduced by metformin. LH plasma level is reduced as a result of decreased pulse amplitude and significant restoration of the menstrual cyclicity in amenorrheic and oligomenorrheic PCOS patients occurs.
- Metformin administration improves reproductive axis functioning in hyperandrogenic PCOS patients by restoring normal ovarian activity and modulating the reproductive axis. It improves menstrual cyclicity through the normalization of the gonadotrophin pulsatile release.[40]

➢ OVULATION INDUCTION

Metformin probably improves ovulation in women with PCOS by reducing gluconeogenesis, improving insulin sensitivity and reducing ovarian androgen production. In a meta-analysis, metformin alone has been shown to have a significant benefit on inducing ovulation in women with PCOS.[41]

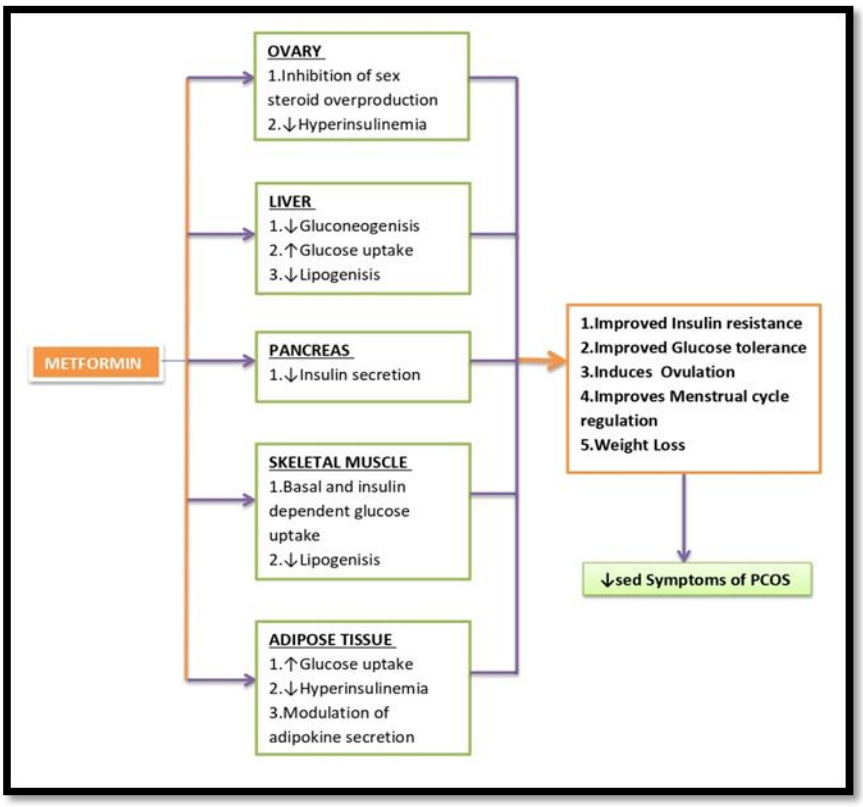

Fig. 4: Mechanisms by which Metformin decreases symptoms of PCOS.

USES OF METFORMIN IN PCOS ASSOCIATED CONDITIONS

1. Obesity

Many individuals struggle to maintain clinically relevant weight loss from life style and bariatric surgery interventions. Long term program from the diabetes prevention program demonstrates that metformin produces durable weight loss, and decreased food intake by metformin is the primary weightloss mechanism.[42]

2. Gestational diabetes

PCOS sufferers have a higher risk of developing GDM in pregnancy (2). Women with PCOS are at increased risk of pregnancy-related complications, including gestational diabetes, pregnancy-induced hypertension, pre-eclampsia and neonatal morbidity. In view of the favourable effects of metformin on metabolic, cardiovascular and thrombotic events in the diabetic population, it would seem feasible that outcomes could be improved in PCOS pregnancies with metformin.[38]

3. Dyslipidaemia

Dyslipidemia, or diabetic dyslipidemia (dyslipidemia in T2DM patients), is an abnormal lipid metabolism that is characterized by elevation of plasma TG, low-density lipoprotein (LDL-C), and reduced plasma levels of high-density lipoprotein cholesterol (HDL-C).

Metformin treatment (2300 mg/day) was found to decrease intestine-derived TG-rich lipoproteins in T2D patients, reducing plasma chylomicrons by 50%, and chylomicron-remnant lipoprotein fractions. Metformin has been found to affect both intestinal and liver tissues resulting in decreased plasma triglycerides, LDL-C, and total cholesterol.[32,43]

PCOS women are reported to have abnormal lipid profiles in comparison to weight- and agematched peers. High triglycerides and low high-density lipoprotein cholesterol (HDL-C) are the most prominent abnormalities that are also strong predictors of CVD and myocardial infarction Metformin can theoretically influence dyslipidaemia either directly through its action on fatty acid metabolism in the liver or indirectly by improving hyperinsulinaemia.[35]

4. Pregnancy loss

PCOS women are at risk of early pregnancy loss, defined clinically as first trimester miscarriage. A number of observational studies have suggested that metformin reduces the risk of pregnancy loss.[44,45]

SIDE EFFECTS OF METFORMIN

- Nausea, vomiting, Anorexia
- Abdominal discomfort, Flatulence, Diarrhea
- Indigestion, Heartburn
- Malabsorption of vitamin B 12, Anaemia
- Unpleasant metallic taste in mouth
- Hairloss,
- Lactic acidosis.[46,47]

CONCLUSION

Polycystic ovary syndrome (PCOS) is a highly prevalent endocrine-metabolic disorder that implies various severe consequences to female health. Although its exact etiology remains elusive, it is known to feature several hormonal disturbances, including hyperandrogenemia, insulin resistance (IR), and hyperinsulinemia. Insulin resistance is a major trigger of metabolic and reproductive abnormalities in women with PCOS. Hyperinsulinemia contributes to hyperandrogenism by augmenting the thecal androgen response to LH and by inhibition of hepatic synthesis of SHBG (Sex hormone binding globulin), resulting in greater concentration of free androgens and appropriate symptoms. Therapy for PCOS becomes necessary in adults in order to induce ovulatory cycles and fertility, and to improve cosmetic appearance (i.e., reduction of hirsutism and acne). Metformin, a biguanide that has been used clinically for many years in the treatment of insulin resistance in type 2 diabetes, and has been used for PCOS in a dose of 500 mg three times a day with a success rate of 20 to 96%. It acts by suppressing hepatic gluconeogenesis, increases insulin sensitivity, enhances peripheral glucose uptake, and decreases insulin induced suppression of peripheral fatty acid oxidation. A meta-analysis of metformin use with and without lifestyle changes in PCOS (including two RCTs in adolescents showed beneficial effects on BMI and menstrual cycles. Metformin is used in women with PCOS and is reported to improve insulin resistance, sex hormone binding globulin (SHBG), hyperandrogenaemia, and ovulation. This review addresses that the treatment with insulin-sensitizing agent, metformin, is effective in many women with PCOS, independent of changes in body weight, in attenuating insulin resistance and hyperandrogenemia and in reversing menstrual abnormalities and chronic anovulation.

REFERENCES

1. Shah R. Emerging Topics in Cardiometabolic and Psychologic Sequelae, Pathogenesis, and Treatment of Polycystic Ovarian Syndrome: A Review. Children (Basel), 2019; 6(8): 89.
2. Jonathan M Lord, Ingrid H K Flight, Robert J Norman. Metformin in polycystic ovary syndrome: Systematic review and meta-analysis. BMJ (Clinical research ed.), 2007; 327: 951- 3.
3. Yau TT, Ng NY, Cheung LP, Ma RC. Polycystic ovary syndrome: a common reproductive syndrome with long-term metabolic consequences. Hong Kong Med J, 2017; 23(6): 622-634.
4. Dennett CC, Simon J. The role of polycystic ovary syndrome in reproductive and metabolic health overview and approaches for treatment.Diabetes Spectr, 2015 May; 28(2): 116 -20.
5. Hifsa Mobeen, Nadeem Afzal and Muhammad Kashif. "Polycystic Ovary Syndrome May Be an Autoimmune Disorder." Scientifica, 2016; 2016: 4071735.

6. Misso ML, Costello MF, Garrubba M, Wong J, Hart R, Rombauts L, Melder AM, Norman RJ, Teede HJ. Metformin versus clomiphene citrate for infertility in non-obese women with polycystic ovary syndrome: a systematic review and meta-analysis. Hum Reprod Update, 2013; 19(1): 2-11.
7. 7.Dokras A, Bochner M, Hollinrake E, Markham S, Vanvoorhis B, Jagasia DH. Screening women with polycystic ovary syndrome for metabolic syndrome. Obstet Gynecol, 2005; 106(1): 131-7.
8. Lo JC, Feigenbaum SL, Escobar GJ, Yang J, Crites YM, Ferrara A. Increased prevalence of gestational diabetes mellitus among women with diagnosed polycystic ovary syndrome: a population-based study. Diabetes Care, 2006; 29(8): 1915-7.
9. Rojas J, Chavez M, Olivar L, Rojas M, Morillo J, Mejías J, Calvo M, Bermúdez V. Polycystic ovary syndrome, insulin resistance, and obesity: Navigating the pathophysiologic labyrinth. Int J Reprod Med, 2014; 2014: 719050.
10. Witchel SF, Oberfield SE, Peña AS. Polycystic Ovary Syndrome: Pathophysiology, Presentation, and Treatment With Emphasis on Adolescent Girls. J Endocr Soc, 2019; 3(8): 1545- 1573.
11. Chang HH, Hsueh YS, Cheng YW, Ou HT, Wu MH. Association between Polymorphisms of OCT1 and Metabolic Response to Metformin in Women with Polycystic Ovary Syndrome. Int J Mol Sci, 2019; 20(7): 1720.
12. Zhao Y, Zhao Y, Wang C, Liang Z, Liu X. DIAGNOSTIC VALUE OF ANTI-MÜLLERIAN HORMONE AS A BIOMARKER FOR POLYCYSTIC OVARY SYNDROME: A META-ANALYSIS UPDATE. Endocr Pract, 2019; 25(10): 1056-1066.
13. Ibanez L, Oberfield SE, Witchel S, et al. An International Consortium Update: Pathophysiology, Diagnosis, and Treatment of Polycystic Ovarian Syndrome in Adolescence. Horm Res Paediatr, 2017; 88(6): 371-395.
14. Nuzhat Shaikh, Roshan Dadachanji, and Srabani Mukherjee. Genetic Markers of Polycystic Ovary Syndrome: Emphasis on Insulin Resistance. International Journal of Medical Genetics, 2014; 2014: 478972.
15. Toscani MK, Mario FM, Radavelli-Bagatini S, Spritzer PM. Insulin resistance is not strictly associated with energy intake or dietary macronutrient composition in women with polycystic ovary syndrome. Nutr Res, 2011; 31(2): 97-103.
16. Krishnan A, Muthusami S. Hormonal alterations in PCOS and its influence on bone metabolism. J Endocrinol, 2017; 232(2): R99-R113.
17. Miller WL. Androgen biosynthesis from cholesterol to DHEA. Mol Cell Endocrinol 2002; 198 (1-2): 7-14.
18. Rosenfield RL, Ehrmann DA. The Pathogenesis of Polycystic Ovary Syndrome (PCOS): The Hypothesis of PCOS as Functional Ovarian Hyperandrogenism Revisited. Endocr Rev, 2016; 37(5): 467-520.
19. Cheng CW, Chang CC, Patria YN, Chang RT, Liu YR, Li FA, Shih HM, Lin CY. Sex hormone-binding globulin (SHBG) is a potential early diagnostic biomarker for gastric cancer. Cancer Med, 2018; 7(1): 64-74.
20. Jing-ling Zhu,Zhuo Chen,Wen-jie Feng, Shuang-lian,Long, Zhong-Cheng Mo. Sex hormone-binding globulin and polycystic ovary syndrome. Clinica Chimica Acta, 2019; 499: 142-148.
21. Baldani DP, Skrgatic L, Ougouag R. Polycystic Ovary Syndrome: Important Underrecognised Cardiometabolic Risk Factor in Reproductive-Age Women. Int J Endocrinol, 2015; 2015: 786362.
22. Sathyapalan T, Atkin SL. Mediators of inflammation in polycystic ovary syndrome in relation to adiposity. Mediators Inflamm, 2010; 2010: 758656.
23. Kahal H, Atkin SL, Sathyapalan T. Pharmacological treatment of obesity in patients with polycystic ovary syndrome. J Obes, 2011; 2011: 402052.
24. Adam Balen. The current understanding of polycystic ovary syndrome. The Obstetrician & Gynaecologist, 2011; 6: 66 - 74.
25. El Hayek S, Bitar L, Hamdar LH, Mirza FG, Daoud G. Poly Cystic Ovarian Syndrome: An Updated Overview. Front Physiol, 2016; 7: 124.
26. Williams T, Mortada R, Porter S. Diagnosis and Treatment of Polycystic Ovary Syndrome. Am Fam Physician, 2016; 94(2): 106-13.
27. Teede H, Deeks A, Moran L. Polycystic ovary syndrome: a complex condition with psychological, reproductive and metabolic manifestations that impacts on health across the lifespan. BMC Med, 2010; 8: 41.
28. Rantonio Simone Lagana, Paola Rossetti, Massimo Buscema, Sandro La Vignera, Rosita Angela Condorelli,, Giuseppe Gullo, Roberta Granese and Onofrio Triolo. Metabolism and Ovarian Function in PCOS Women: A Therapeutic Approach with Inositols. International Journal of Endocrinology, 2016; 2016: 1-9.
29. Spinedi E, Cardinali DP. The Polycystic Ovary Syndrome and the Metabolic Syndrome: A Possible Chronobiotic – Cytoprotective Adjuvant Therapy. Int J Endocrinol, 2018; 2018: 1349868.
30. Unfer V, Nestler JE, Kamenov ZA, Prapas N, Facchinetti F. Effects of Inositol(s) in Women with PCOS: A Systematic Review of Randomized Controlled Trials. Int J Endocrinol, 2016; 2016: 1849162.
31. Geller DH, Pacaud D, Gordon CM, Misra M; of the Drug and Therapeutics Committee of the Pediatric Endocrine Society. State of the Art Review: Emerging Therapies: The Use of Insulin Sensitizers in the Treatment of Adolescents with Polycystic Ovary Syndrome (PCOS). Int J Pediatr Endocrinol, 2011; 2011(1): 9.

32. Zhou J, Massey S, Story D, Li L. Metformin: An Old Drug with New Applications. Int J Mol Sci, 2018; 19(10): 2863.
33. Genazzani AD, Ricchieri F, Lanzoni C. Use of metformin in the treatment of polycystic ovary syndrome. Womens Health (Lond), 2010; 6(4): 577-93.
34. Mathur R, Alexander CJ, Yano J, Trivax B, Azziz R. Use of metformin in polycystic ovary syndrome. Am J Obstet Gynecol, 2008; 199(6): 596-609.
35. Lashen H. Role of metformin in the management of polycystic ovary syndrome. Ther Adv Endocrinol Metab, 2010; 1(3): 117-28.
36. Velazquez EM, Mendoza S, Hamer T, Sosa F, Glueck CJ. Metformin therapy in polycystic ovary syndrome reduces hyperinsulinemia, insulin resistance, hyperandrogenemia, and systolic blood pressure, while facilitating normal menses and pregnancy. Metabolism, 1994; 43(5): 647-54.
37. Howard Craig Zisser.Polycystic ovary syndrome and pregnancy: is metformin the magic bullet?. Diabetes Spectrum, 2007; 20(2): 85-89.
38. Diamanti-Kandarakis E, Christakou CD, Kandaraki E, Economou FN. Metformin: an old medication of new fashion: evolving new molecular mechanisms and clinical implications in polycystic ovary syndrome. Eur J Endocrinol, 2010; 162(2): 193-212.
39. Wang YW, He SJ, Feng X, Cheng J, Luo YT, Tian L, Huang Q. Metformin: a review of its potential indications. Drug Des Devel Ther, 2017; 11: 2421-2429.
40. Maha Yousef Soliman Omran. Metformin and polycystic ovary syndrome. Int J Health Sci (Qassim), 2007; 1(1): 75-80.
41. Barbieri RL. Clomiphene versus metformin for ovulation induction in polycystic ovary syndrome: the winner is ... J Clin Endocrinol Metab, 2007; 92(9): 3399-401.
42. Malin SK, Kashyap SR. Effects of metformin on weight loss: potential mechanisms. Curr Opin Endocrinol Diabetes Obes, 2014; 21(5): 323-9.
43. Van Stee MF, de Graaf AA, Groen AK. Actions of metformin and statins on lipid and glucose metabolism and possible benefit of combination therapy. Cardiovasc Diabetol, 2018; 17(1): 94.
44. Kumar P, Khan K. Effects of metformin use in pregnant patients with polycystic ovary syndrome. J Hum Reprod Sci, 2012; 5(2): 166-9.
45. Nawaz FH, Rizvi J. Continuation of metformin reduces early pregnancy loss in obese Pakistani women with polycystic ovarian syndrome. Gynecol Obstet Invest, 2010; 69(3): 184-9.
46. Polycystic Ovary Syndrome Symptoms https://www.verywellhealth.com/pcos-overview-4014672.
47. Nasri H, Rafieian-Kopaei M. Metformin: Current knowledge. J Res Med Sci, 2014 Jul; 19(7): 658-6.