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MANAGEMENT AND PATHOPHYSIOLOGY OF POLYCYSTIC OVARIAN SYNDROME IN WOMEN WITH INFERTILITY – A REVIEW.

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ABSTRACT

PCOS (polycystic ovarian syndrome) is a complex condition caused by interactions among genetic, environmental, hormonal and neuroendocrine factors. Approximately 5% women causing PCOS due to anovulation. Which can occur with hyperandrogenism, hyperinsulinemia, or gonadotropin abnormalities. PCOS is most prevalent cause of infertility in women due to anovulation. There are variety of treatment options available in which majority of them based on ovarian stimulation with FSH, lowering the level of insulin in body and a drop in LH level. Ovulation induction like CC as well as aromatase inhibitors (letrozole) considered as first line of defense to treat the PCOS as monotherapy. If patients do not respond with these therapies, then direct FSH stimulation with low doses need to administer. Metformin as well as inositol also used to treat this syndrome caused by hyperinsulinemia. The combination therapy of Metformin with CC as well as with gonadotropin give better response in treatment of PCOS compare with metformin alone.

Key words- PCOS, Anovulation, Hyperandrogenism, hyperinsulinemia, Gonadotropin abnormalities, Infertility, FSH, LH, Clomiphene citrate, Letrozole, Metformin.

Abbreviations- PCOS (Polycystic ovarian syndrome), CC (Clomiphene Citrate), LH (Luteinizing Hormone), FSH (Follicle Stimulating Hormone) , OHSS (Ovarian Hyper Stimulation Syndrome), DM (Diabetes mellitus), AMH (Anti Mullerian Hormone), BMI (Body Mass Index).

INTRODUCTION- PCOS (polycystic ovarian syndrome) is defined as the hormonal disorder that

affect a large percentage of the women in reproductive age. This disorder is also known as Stein-Leventhal disease, Realistic ovarian hyperandrogenism, Ovarian hypothecosis, Sclerocystic ovary disease and Polycystic ovary malady. This Disease was first discovered in 1935 by American Gynecologist Irving F Stein and Michael L Leventhal, who gave it the name Stein Leventhal disorder [1]. It describes a syndrome in which one or both ovaries develop an estimated 10 tiny cysts with a diameter ranging 2 to 9mm in ovarian volume at least 10ml exceed by single ovary.

Around 75-80% women with infertility due to anovulation have polycystic ovarian syndrome [2]. Most of females having anovulation due to PCOS experiences an abnormal menstruation, Hyperandrogenism, Excess growth of hairs on the body or scalp (Hirsutism), Acne, Hyperinsulinemia, Pelvic pain and difficulties getting pregnant. According to several studies following are the main symptoms of this syndrome.

Abnormal morphology of the ovary- according to Rotterdam study PCO morphology is a minimum of follicle per ovary and in an ovarian volume of >10cc in at least one ovary.[1]

1) Abnormal Steroidogenesis- It include Increased androgen production in ovaries as well as increased production of estradiol and progesterone.
2) Hyperinsulinemia-It include Insulin resistance in body.
3) Abnormal Gonadotropin secretion- Around 40%of women, ultrasonically identified PCO, the most prevalent symptom is elevated serum LH concentration as well as decreased endogenous action of FSH.[1]

Women with PCOS Have proven, greater chances of acquiring type 2 DM, Hypertension, and increased risk of cardiovascular disease as well as anxiety, depression, reduced quality of life, body image and eating problems are all psychological characteristics of this syndrome, if not treated. This disease occurs due to number of follicles per ovary each month growing from average range of 6-8 to double-triple and more. Obesity, Hyperandrogenism and having an increased level of luteinizing hormone (LH), all have negative impact on fertility.[20] The fundamentals of treatment for those who appears with anovulatory infertility due to PCOS need to optimize the situation first. Management can be done by reduction of body weight and ovulation induction therapy (includes Clomiphene citrate, Letrozole, Gonadotropin etc.) [28] which may improve the endocrine profile as well as ovulation in obese and normal women.[6]

The goal is to produce consistent unifollicular ovulation while avoiding ovarian hyperstimulation syndrome (OHSS) and possibilities of having numerous pregnancies.

Pathophysiology of PCOS

PCOS is a complex disorder that can arises from a variety of factors, like Hormonal, Neuroendocrine, genetic and environmental factors that may contribute to the development of this polycystic ovarian syndrome.[20]

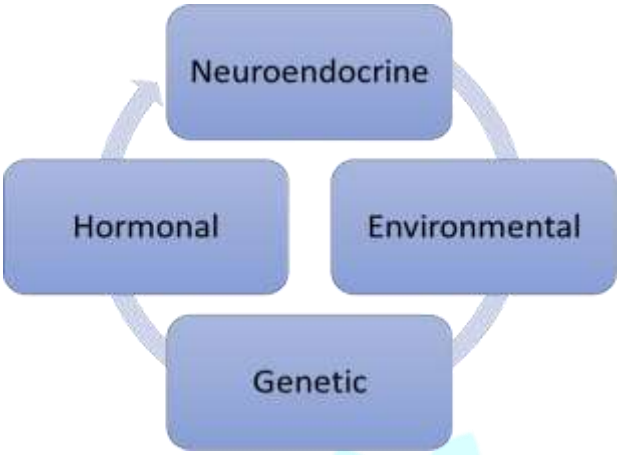

Figure.1

Hormonal factors

Development of this disease is triggered by a variety of hormones. A lot of research has been done on the involvement of Anti-mullerian hormone (AMH) in development of PCOS.[20] The AMH aid in the development of both male and female reproductive organs. It also aids in the regulation of other hormones that act on the ovaries during the menstrual cycle to cause follicles and eggs to grow.[21] AMH level in the blood can be measured to aid in the diagnosis of infertility and other disease including PCOS. This hormone is generally produced in the male fetus and aids in the mullerian ducts deterioration and ovarian granulosa cells generate it in females.

AMH reduces the sensitivity of growing follicles to follicle stimulating hormone (FSH) in the ovaries. It also disrupts the natural functioning of the ovaries and the aromatase enzyme. As a result, primordial follicle's initiation is inhibited. Durlinger et. al. investigated the impact of AMH on the recruitment of primordial follicles in a study [3].He carried out his study on ovaries from 2 days old mice which harvested and cultured. After 2-4 days of culturing and harvesting these ovaries. When ovaries exposed to AMH were compared with control ovaries the number of developing follicles was found to be lower.[3] As a result, AMH appears to have the ability to directly atler the primordial follicles.

Insulin is another hormone that is hypothesized to play a key role in the development of this syndrome. Various investigation have discovered that many PCOS women have higher insulin resistance that is higher than what their BMI predicts.[29] Insulin resistance is found in 50-70% of these women with PCOS[4] .Insulin resistance lead to compensatory hyperinsulinemia, which is responsible for many of PCOS's clinical characteristic. Majority of women with PCOS are young and as a result of their insulin who faces insulin resistance which develops compensatory

hyperinsulinemia, and their impaired glucose tolerance is more easily detected by oral or intravenous glucose testing than by basal glucose monitoring.[4] Insulin resistance is a significant component to the pathophysiology of PCOS.[1] IR causes elevated blood insulin and glucose level as well as increased oxidative stress which generally leads to the development of the various factors observed in PCOS. Insulin malfunction contributes to insulin signaling abnormalities or insulin receptor that are not functioning normally. As a result, hyperinsulinemia develops, as well as decreased hepatic insulin clearance. Hyperinsulinemia is also a major factor in the development of this syndrome, via increasing the production of testosterone in ovarian cell or reducing the level of sex hormone binding protein (SHBP) In the blood.[1] As well as insulin's action on the hypothalamus and pituitary gland have the ability to impact gonadotropin level. Hyperinsulinemia stimulates androgen synthesis by the adrenal gland which is regulated by the adrenocorticotropic hormone (ACTH).[20]

Insulin is also involved with gonadotropin in causing the granulosa cells in the ovary to generate steroids.[30] It has also been noted that with increased insulin level the Luteinizing hormone (LH) makes the granulosa cells more sensitive and responsive, which hypothesized to be the cause of anovulation in the people with PCOS.[4] It observed that the normal ovarian follicles only respond to the Gonadotropin LH when they reach to ideal size of 10mm while the ovaries of the PCOS individuals respond to Gonadotropin LH at very smaller size than optimal size (i.e 4.5mm).[1] This difference can be observed due to hyperinsulinemia in PCOSpatients.[20]

Neuroendocrine factors

Women with PCOS had higher level of LH pulse frequency, LH pulse amplitude and decreased FSH.[6] According to numerous research its proven that PCOS patient had a greater amount of AMH (Anti-mullerian hormone) than the control group.[3] Several in vivo investigations were carried out which shows the effect of AMH on secretion of LH via activation of Gonadotropin releasing hormone (GnRh) secreting in hypothalamic neurons.[8] AMH raises LH levels in hypothalamus binding with AMH receptors on GnRh neurons as well as AMH decreases the FSH release in women with PCOS.[6] Increasing LH secretion while decreasing FSH is a classical feature of the PCOS.

Kisspeptide, neurokinin B, and Dynorphin are peptides released by the neurons in the arcuate nucleus of the hypothalamus.[6] These neurons named as KNDy neurons because of the calcolization of these three peptides and their functions in episodic GnRh secretion. KNDy neurons are frontrunners for being the hypothalamic GnRh pulse generator which leads to elevate the LH in secretion, which is the main characteristics to development of PCOS in women.

Environmental factors

PCOS related environmental variables can be classified as prenatal and postnatal. Where prenatal involves fetal programming and postnatal involves diet, obesity, sedentary lifestyle, environmental

toxin and prescription drugs. Environmental exposure may be influenced by dietary choices, exercise and cultural, social as well as economic factors.[20]

According to various research it proven that, PCOS may have a non genetic inheritance pattern among population with bad lifestyle like high saturated fat diet, sedentary life style, alcoholism and smoking. It leads to change in fetal placental unit, the beginning of the IUGR (intra uterine growth restriction) and the prevalence of SGA (small for gestational age) babies in such population compared to population with healthy lifestyle.[31] In reproductive age women, hyperinsulinemia and visceral adiposity are more likely to develop to higher prevalence of insulin resistance(IR), systemic arterial hypertension(SAH), and hyperandrogenism. Numerous studies suggests that women who were born SGA have higher risk of placental abnormalities and they give delivery of SGA babies during pregnancy. This condition can not consider as genetic factor of PCOS. In this case if women with SGA will maintain a healthy lifestyle throughout their childhood to their reproductive age, then these women would not go

through any placental abnormalities as well as newborn baby will be AGA (appropriate gestational age).[19]

The impact of lifestyle changes on visceral adiposity demonstrates the significance of environmental factors in the development of the PCOS. These are very common comorbidity in women with PCOS. So that the first line of defense is body weight loss in PCOS affected obese women.[12] Reduction of 2-5% body weight in PCOS affected obese women decreases hyperinsulinemia, raises sex hormone biding globulin levels (SHBG), decreases androgen level, restore the ovulatory cycles and improves clinical hyperandrogenism and metabolic disorder including dyslipidemia.[29] So high saturated fat diet as well as sedentary life style are major environmental factors involved in the development of the PCOS and its metabolic implication is particularly obesity.

Genetic factors

PCOS has been proved to have a hereditary component, according to numerous studies. PCOS affect around 20-40% of the first-degree female relatives of individuals with these condition [4]. Family members have a higher prevalence of PCOS compared to normal population. PCOS heritability of 0.79 according to Dutch twin family study, indicating that genetic factor plays key role in syndromes development.[4[In family of women with PCOS has heritable component to hyperandrogenism, insulin resistance (IR), hyperinsulinemia.

Candidate gene association approaches were used in most PCOS genetic research, in which variation in gene of interest are genotyped and their relationship to PCOS is investigated. As well as proven, that like DM2 and IBD, and PCOS can appears to be inherited as common complicated condition.[1] There are various genetic variation that have a moderate effect when paired with risk increasing lifestyle and environmental variables.

Despite the fact that there have been many association studies, attempts those the good gene replication results are extremely rare. Gene linked to PCOS or PCOS like symptoms are fibrillin 3 (FBN3) and 17-hydroxysteroid dehydrogenase are two of its component features that have replicate and cause PCOS.its yet unclear that how genetic factors involves in the development of PCOS in women.[11] So compared to other common illness like type 2 diabetes mellitus other genetic acquired diseases, PCOS has been very low chances to acquire genetically.

Management of PCOS associated infertility Non-

Pharmacological Management

Life style changes – weight reduction, a nutrious diet and regular physical activity are all examples of lifestyle modification that can help to treat a women with PCOS. Women with PCOS generally advised to lose weight as a first line of treatment.[25] A good diet and regular physical activity are known to aid in the reduction of Insulin resistance and hyperandrogenism, as well as optimizations of hormonal problems and cardiovascular problems.[12] Insulin resistance affect around 50-80% of the females experiencing PCOS and most of these womenare obese.[12]

So far, there is no conclusive evidence that the lifestyle changes affect reproductive outcomes. According to certain research weight loss with PCOS has been linked to irregular ovulation and they give better response to ovulation induction medicines as well as in pregnancy and life birth rates. Obesity and hyperinsulinemia can be successfully treated and the negative effect of both the conditions which are numerous can be reversed, improving the selected outcome. Losing weight may alter this process by enhancing ovarian function and the associated hormonal imbalances just as heavy weight displace and exaggerates the manifestations of irregularity. In obese woman with PCOS losing nearly 5-10% of their body weight is required to restore reproductive function in 88 to 100% of them after 6 months of weight reduction.[29] reducing Weight has the undeniable advantage in terms of effectiveness, cost and adverse effect and should be the first line of defense for a over weight women with PCOS related to anovulatory infertility.

PHARMACOLOGICAL MANAGEMENT-

OVULATION INDUCTION- ovulation inducement is the foundation of infertility treatment for females experiencing PCOS.[2] On the basis of several research, it's proven that 70% of females having PCOS affected with oligo ovulation, tubal patency testing such as hysterosalpingography should be contemplated as earlier to ovulation inducement in female having PCOS and infertility due to anovulation along with normal Semen analysis. In 20% of infertile couple's tubal disease is a causative factor.[2]

Letrozole, clomiphene and gonadotropins are the commonly used medication for inducement of ovulation, in which letrozole is preferred as a first line therapy for PCOS in infertile women.[2]

SELECTIVE ESTROGEN RECEPTOR MODULATOR (SERMs)- Clomiphene citrate is an estrogenic receptor modulator has been traditionally used for the women having missing or abnormal ovulation.[3] It is administered at a dose of 50- 250 mg per day for five days, starting with the lowest dose that is 50 mg per day and gradually raised to 50 mg every next day until an ovulatory cycle is obtained.[3] In various cases use of starting doses 100 mg per day has found no therapeutic affect as well as increasing the daily dose with 150 mg does not appear to have significant boost in ovulation rate as follicular recruitment in such cases which not responded with these doses, resistance to clomiphene identified.[2,3] Normally It takes 3-6 ovulatory cycles to determine if clomiphene will result in pregnancy or not. According to studies approximately 75% of clomiphene induced pregnancy develops within the first three cycles of therapy.[1]

Clomiphene citrate is an anti- estrogen that works by inhibiting the receptors in hypothalamus which causes increase in the pulse amplitude of gonadotropin releasing hormone (GnRH).[16] as well as interior pituitary synthesis of follicular stimulating hormone (FSH) and Luteinizing hormone (LH), which stimulates follicle development in the women with infertility associated with PCOS.[3] The anti-estrogenic action can also influence the endometrium and cervical mucus potentially preventing implantation by suppressing endometrial proliferation.

According to Kafy and Tulandi, CC is correlated with a greater risk of multiple featus development, approximately 5 to 7% and 0.3% respectively.[3,2] Hance ultrasound screening technique is used to detect multifolicular development. Hot flushes, nausea, breast soreness, and impaired eyesight are among of the common side effect of CC.[1]

Clomiphene citrate could be used with metformin in women with PCOS and who have resistance with clomiphene citrate. Cochrane study by Morley et al, reported that an enhanced pregnancy and ovulation rate with combined therapy of metformin and clomiphene citrate over single therapy of CC , and suggesting that combined medication may have a helpful in the treatment of PCOS associated with Insulin resistance.

AROMATASE INHIBITORS –Letrozole- Androgen to estrogen conversion is carried out by enzyme Aromatase, while letrozole acts by preventing androgen to be converted into estrogen, As a result it is used to treat PCOS.[16] Letrozole treats reproductive issues directly by negative feedback loop that exists between the ovaries, brain and pituitary gland. mode of action of this drug is to stimulates and increase in FSH levels in the blood plasma which increases follicle formation, maturation and ovulation.[12] Letrozole is more effective then CC in treating PCOS

related reproductive problems because it is linked to better gestational outcomes and the greater extent of live birth.[3] Despite the fact that the World Health Organization recommends letrozole for ovulation induction as a first line of defense. Letrozole has been suggested as an alternative to clomiphene citrate in several guidelines of WHO because it has a shorter Half Life then the other medicine, so it is unlikely to cause severe side effects. When compared to CC, it has a decreased

chance of multiple pregnancy [4,3,28].

Standard dose of letrozole is 2.5mg per day for 5 days and ultrasound follicular tracking is used to detect the ovulation.[16] Ovulation can be initiated using human chronic gonadotropin and final intercourse which leads to the follicular achievement of a diameter of at least 18 mm. After this Trigger ovulation should happen 36 to 48 hours later.[3] If ovulation does not occur in the next cycle the doses might be doubled from the prior dose.

GONADOTROPINS- In women with PCOS, gonadotropin therapy can be utilised as a second line pharmacological treatment who have failed to ovulate after using SERMs and Aromatase inhibitors may benefit from low dose FSH stimulation.[3] It necessities prior gonadotropin stimulation experience with close monitoring and the possibility of converting to IVF if multimolecular development occurs. The usual initial dose is 50 – 75IU for 2 weeks followed by a weekly increase of those with 25 to 37IU if there is no response.[16] If follicle develops with the given dose the same is needed to be used until the size of the follicle reaches to 18 to 20mm.[2] If there are three or more follicles greater then 14 mm in diameter HCG should not be given, to avoid the possibility of multiple pregnancy and OHSS.[2]

Single live birth rate of roughly 75 to 80% can be achieved with an ovulation induction strategy that uses clomiphene citrate as a line treatment and gonadotropin as the second line treatment for PCOS.[16] If pregnancy does not happen after 6 ovulatory cycles in a woman under the age of 25 or after 12 cycles in women over the age of 25.[12] Therefore, in this case anovulation is unlikely to be causes of infertility in the couple. Assistant reproduction example IVF is recommended if there is no other explanation for this condition is established.

METFORMIN- Metformin is synthetic generated by biguanide that is most recommended and cost effective first line oral medication for the treatment of type 2 Diabetes mellitus.[17] It's major sight of action is in the liver where it lowers hepatic glucose synthesis which lowers blood lipid level and enhances insulin mediated glucose absorption by the liver and skeletal muscle and reduces substrate availability for gluconeogenesis.[1] As a result it lowers serum insulin which may help with PCOS symptoms in women with hyperinsulinemia

Insulin resistance and hyperinsulinemia are the primary causes of anovulation in people with PCOS. Obese people can reverse their PCOS symptoms by losing weight, however those who unable to reduce or who are standard weight or underweight, but hyperinsulinemia should take an insulin sensitizing drug like Metformin and inositol to reduce insulin level in body.[10] Early trials of metformin's usage in the treatment of PCOS revealed that it improved reproductive functions and may have long term health advantages.[2] In fact, Metformin may operate both indirectly by lowering systemic insulin level and directly with in the ovary.

Numerous research was reported on the impact of metformin in women with PCOS at doses ranging from 1500-2550mg per day.[17] These investigations have shown significant improvements

in insulin concentration, insulin sensitivity, and serum androgen concentration as well as lower LH and higher SHBG levels. [4,12]. Metformin has been shown to restore normal menstrual periods in the vast majority of published studies, with ovulation being restored in 78-96% of patient [4,5,16].

According to randomized control trial Metformin significantly increased ovulation and conception rates with clomiphene citrate in the treatment of PCOS, In women who are resistant with mono therapy of clomiphene citrate. In a major trial, its proven that several anovulatory obese women with PCOS who had not ovulated after 35 days on metformin, gave positive result with combination therapy of 50mg of clomiphene and metformin daily for 5 days [7].

The evidence suggests that use of metformin alone or in combination with CC or gonadotropins is efficient and secure for inducing ovulation in females who have high insulin level due to PCOS. It is still unclear, whether metformin, which is thought to have a direct androgen reduction effect on the ovary, will be beneficial to all those women who have PCOS, who wants to conceive. Metformin is not only appears to be secure during pregnancy, but preliminary study clearly shows that, this method can significantly reduce the substantial risk of miscarriage in women having PCOS.[17] Not yet fully described but future research will confirm that teratogenicity of metformin and its positive effect on miscarriage rates.[10,17]

Inositol (hexahydroxy cyclohexane)—It is a six- carbon ring chemical compound with 9 stereoisomeric forms with a hydroxyl group attached with every carbon atom of the ring[4,6,7]. Myoinositol (MI) and D-chiro -inositol (DCI) are two of these insulin sensitizing compounds that have diverse biological activities. MI regulates glucose absorption and FSH signaling in the ovary where as DCI reduces insulin androgen production [11,20,8]. The inositol MI and DCI have been shown to reduce insulin resistance, increase ovarian function and decrease androgen levels in women with PCOS. DCI seems to play a role in insulin metabolism, in women with PCOS. DCI therapy has been shown to lower insulin levels, triglycerides and blood pressure.[11]

In overweight women with PCOS, MI has been shown to increase the number of good quality oocytes, normal administration dose of MI is about 2g over the course of 3-6 months.[4] The impact of DCI on metabolic, endocrine and reproductive factors in PCOS has been examined by a number of researchers. Lean women with PCOS were given 600mg DCI per day for 6-8 weeks had lower insulin and free testosterone levels as well as lower systolic and diastolic blood pressure and serum lipids.[20] With use of DCI, there is a greater rate of ovulation noted.

Vitamin D – Vitamin D deficiency or inadequacy may affects 45 to 90% of women with reproductive age [4,19]. Both PCOS as well as vitamin D insufficiency have been linked to IR. Vit. D insufficiencies linked to significantly lower rates of ovulation, pregnancy, and ultimately, a lower likelihood of live birth in women having PCOS who received ovarian stimulation for treatment of infertility. It is suggested as a viable treatment adjuvant for PCOS related ovulatory failure and metabolic disorder.

Medroxyprogesterone Acetate – The female hormone medroxyprogesterone acetate (MPA) is a progestin that may control ovulation and menstruation. This can be used to treat a variety of issues, such as amenorrhea or dysfunction of uterine bleeding.[28] It is also effective in the treatment of endometriosis as well as lowers the risk of uterine cancer. In PCOS patients, MPA offers the extra benefit of increasing insulin sensitivity and blood lipid profile.

Laparoscopic ovarian drilling (LOD)- It is a surgical method of ovulation induction for women who are resistant with all the pharmacological therapy of ovulation induction.[2,3,4] General mechanism of LOD is to restore ovulatory function in women by destruction of androgen producing tissues leading to decrease ovarian androgen production and peripheral androgen level as well as estrogen conversion.[20] This surgical treatment can help lowering LH and testosterone level in the blood to treat infertility in women.[3]

Sr.No	Drugs	Class	Dose	Indication
1	Clomiphene Citrate	SERMs	50-250mg/day	Ovulation induction
2	Letrozole	Aromatase Inhibitors	2.5mg/day	Ovulation induction
3	Gonadotropins	Hormonal therapy	50-75IU	Ovulation inducement
4	Metformin	Biguanides	1500-2550mg/day	Reduce insulin level
5	Inositol	Hormonal therapy	600mg/day	Insulin Resistance
6	Vitamin-D	Vitamin supplement	4000IU//day	VitaminD insufficiency
7	Medroxyprogesterone Acetate	Hormonal therapy	10-20mg/day	Oligomenorrhea and hirsutism

Table.1

Conclusion

PCOS is a severe health risk for women which associated with long term risk of glycemic abnormality type 2 diabetes mellitus, cardiovascular disease, obstetrical problem and affective disorder (like anxiety, depression). Although the exact pathophysiology of PCOS is still unknown, but it has a multifactorial etiology that can Aries as a result of hormonal, neuroendocrine, genetic or environmental causes. Management includes non-pharmacological, pharmacological as well as surgical methods are used to treat this syndrome. Although the clinical appearance of PCOS in adolescent girls and adult women are differ significantly. Pharmacological therapy can surely result in better clinical outcomes, such as CC, letrozole, gonadotropins are used as first line of defense for the treatment of PCOS in women with infertility. Metformin and inositol is used as second line of defense to treat this syndrome. The combination therapy of CC and metformin as well as

gonadotropin and metformin are more useful in the treatment of PCOS induced infertility compared to monotherapy of CC, gonadotropin or metformin.

References

1. Homburg, R. (2003). The management of infertility associated with polycystic ovary syndrome. *Reproductive Biology and Endocrinology*, *1*(1), 1-9.
2. Homburg, R. (2004). Management of infertility and prevention of ovarian hyperstimulation in women with polycystic ovary syndrome. *Best Practice & Research Clinical Obstetrics & Gynaecology*, *18*(5), 773-788.
3. Homburg, R. (2007). Ovulation induction for women with polycystic ovary syndrome. *U: Polycystic Ovary Syndrome. Kovacs G, Norman R, urednici, Cambridge*, 140-158.
4. Goodarzi, M. O., Dumesic, D. A., Chazenbalk, G., & Azziz, R. (2011). Polycystic ovary syndrome: etiology, pathogenesis and diagnosis. *Nature reviews endocrinology*, *7*(4), 219-231.
5. Azziz, R., Carmina, E., Dewailly, D., Diamanti-Kandarakis, E., Escobar-Morreale, H. F., Futterweit, W., ... & Witchel, S. F. (2009). The Androgen Excess and PCOS Society criteria for the polycystic ovary syndrome: the complete task force report. *Fertility and sterility*, *91*(2), 456-488.
6. Gorry, A., White, D. M., & Franks, S. (2006). Infertility in polycystic ovary syndrome. *Endocrine*, *30*(1), 27-33.
7. Norman, R. J., Dewailly, D., Legro, R. S., & Hickey, T. E. (2007). Polycystic ovary syndrome. *The Lancet*, *370*(9588), 685-697.
8. Diamanti-Kandarakis, E., & Dunaif, A. (2012). Insulin resistance and the polycystic ovary syndrome revisited: an update on mechanisms and implications. *Endocrine reviews*, *33*(6), 981-1030.
9. Bozdag G, Mumusoglu S, Zengin D, Karabulut E, Yildiz BO. The prevalence and phenotypic features of polycystic ovary syndrome: a systematic review and meta-analysis. Hum Reprod. 2016;31:2841–2855.
10. Escobar-Morreale HF. Polycystic ovary syndrome: definition, aetiology, diagnosis and treatment. Nat Rev Endocrinol. 2018;14:270–284.
11. Rosenfield, R. L., & Ehrmann, D. A. (2016). The pathogenesis of polycystic ovary syndrome (PCOS): the hypothesis of PCOS as functional ovarian hyperandrogenism revisited. *Endocrine reviews*, *37*(5), 467-520.
12. McKenna, T. J. (1988). Pathogenesis and treatment of polycystic ovary syndrome. *New England Journal of Medicine*, *318*(9), 558-562.
13. Malina, A., Błaszkiewicz, A., & Owczarz, U. (2016). Psychosocial aspects of infertility and its treatment. *Ginekologia Polska*, *87*(7), 527-531.
14. Hocaoglu, C. (2019). The psychosocial aspect of infertility. *Infertility, Assisted Reproductive Technologies and Hormone Assays*, *65*.
15. Nasim, S., Bilal, S., & Qureshi, M. (2019). Psycho-social aspects of infertility-a review of current trends. *The Professional Medical Journal*, *26*(09), 1537-1541.
16. Johansson, J., Redman, L., Veldhuis, P. P., Sazonova, A., Labrie, F., Holm, G., ... & Stener-Victorin, E. (2013). Acupuncture for ovulation induction in polycystic ovary syndrome: a randomized controlled trial. *American Journal of Physiology-Endocrinology and Metabolism*, *304*(9), E934- E943.
17. Nestler JE, Jakubowicz DJ, Evans WS and Pasquali R: Effects of metformin on spontaneous and clomiphene-induced ovulation in the polycystic ovary syndrome. Fertil Steril 2002.
18. McKenna, T. J. (1988). Pathogenesis and treatment of polycystic ovary syndrome. *New England Journal of Medicine*, *318*(9), 558-562.
19. Hill, K. M. (2003). Update: the pathogenesis and treatment of PCOS. *The Nurse Practitioner*, *28*(7),8-17.

20. Witchel, S. F., Oberfield, S. E., & Peña, A. S. (2019). Polycystic ovary syndrome: pathophysiology, presentation, and treatment with emphasis on adolescent girls. *Journal of the Endocrine Society*, *3*(8), 1545-1573.

21. Witchel, S. F., Oberfield, S. E., & Peña, A. S. (2019). Polycystic ovary syndrome: pathophysiology, presentation, and treatment with emphasis on adolescent girls. *Journal of the Endocrine Society*, *3*(8), 1545-1573.

22. Rothenberg, S. S., Beverley, R., Barnard, E., Baradaran-Shoraka, M., & Sanfilippo, J. S. (2018). Polycystic ovary syndrome in adolescents. *Best Practice & Research Clinical Obstetrics & Gynaecology*, *48*, 103-114.

23. Peña, A. S., Witchel, S. F., Hoeger, K. M., Oberfield, S. E., Vogiatzi, M. G., Misso, M., ... & Teede, H. (2020). Adolescent polycystic ovary syndrome according to the international evidence-based guideline. *BMC medicine*, *18*(1), 1-16.

24. Thiam, C. A., Antoine, M. M., & Antoine-Frank, C. D. (2021). Polycystic ovarian syndrome: pathogenesis and management. *nature*, *7*, 8.

25. Sadrzadeh, S., Painter, R. C., & Lambalk, C. B. (2016). Developmental origins of polycystic ovary syndrome (PCOS), a case control study comparing birth weight in women with PCOS and control group. *Gynecological Endocrinology*, *32*(10), 856-859.

26. Maqbool, M., Dar, M. A., Gani, I., & Geer, M. I. (2019). Insulin resistance and polycystic ovary syndrome: a review. *Journal of drug delivery and therapeutics*, *9*(1-s), 433-436.

27. Azziz, R., Carmina, E., Dewailly, D., Diamanti-Kandarakis, E., Escobar-Morreale, H. F., Futterweit, W., ... & Witchel, S. F. (2009). The Androgen Excess and PCOS Society criteria for the polycystic ovary syndrome: the complete task force report. *Fertility and sterility*, *91*(2), 456-488.

28. Cunha, A., & Póvoa, A. M. (2021). Infertility management in women with polycystic ovary syndrome: a review. *Porto Biomedical Journal*, *6*(1).

29. Ibáñez, L., Oberfield, S. E., Witchel, S., Auchus, R. J., Chang, R. J., Codner, E., ... & Lee, P. A. (2017). An international consortium update: pathophysiology, diagnosis, and treatment of polycystic ovarian syndrome in adolescence. *Hormone research in paediatrics*, *88*, 371-395.

30. Baptiste, C. G., Battista, M. C., Trottier, A., & Baillargeon, J. P. (2010). Insulin and hyperandrogenism in women with polycystic ovary syndrome. *The Journal of steroid biochemistry and molecular biology*, *122*(1-3), 42-52.

31. Parker, J., O'brien, C., Hawrelak, J., & Gersh, F. L. (2022). Polycystic ovary syndrome: An evolutionary adaptation to lifestyle and the environment. *International Journal of Environmental Research and Public Health*, *19*(3), 1336.