Journal of Cardiovascular Disease Research
ISSN: 0975-3583, 0976-2833 VOL 12, ISSUE 04, 2021

Study of Infertility in Polycystic Ovary Syndrome

Amal Mohamed Al Anwar, Mohamed Lotfy Mohamed El Sayed , Ameerah Mohammed Alsheebani Salim, Hoda Sibai Abd Al Salam
Department of Obstetrics and Gynecology, Zagazig University Hospital, Egypt.
Corresponding Author: Ameerah Mohammed Alsheebani Salim
Email: Amiramh545@gmail.com

Abstract

Background: Polycystic ovarian syndrome (PCOS) is a frequently occurring metabolic and reproductive endocrinopathy. Young women with PCOS mainly present with reproductive problems such as hyperandrogenism (HA), menstrual irregularities, infertility and chronic anovulation. Infertility increases 10 folds in women with PCOS and affects up to 40%. PCOS reduces fertility due to associated endocrine, metabolic and gynecological abnormalities that impact on the quality and function of the ovary. Clinically, PCOS is characterized by either oligoovulation or anovulation and HA that may cause infertility, and other related metabolic disorders. The infertile patients with PCOS had statistically higher occurrence of an ovulatory cycle with oligomenorrhoea, hirsutism and serum testosterone levels compared to infertile women with normal ovaries.

Keywords: Infertility, Polycystic Ovary Syndrome

Background

Polycystic ovary syndrome (PCOS) is a common cause of female infertility and affects 15–25% of women, based on the Rotterdam criteria of PCOS. **(1, 2)**

Ovulation disorders are the cause of infertility in around 25% of couples and PCOS is the major cause of anovulatory infertility, accounting for approximately 70% of all cases**. (3).**

❖ ***PCOS-Related Factors of Infertility:***

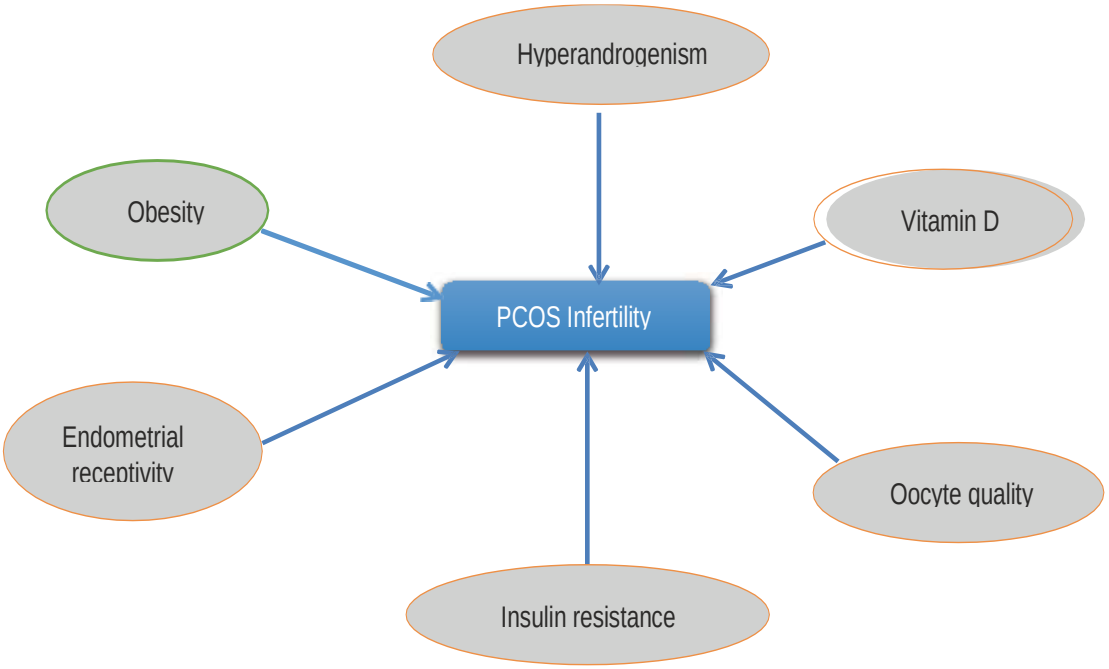

Fig.1- Main PCOS-related factors that may contribute to infertility in women with the syndrome**.** ***(4)***

1. Hyperandrogenism:

Hyperandrogenism is the main feature of PCOS. According to the Rotterdam criteria, PCOS can be defined in the absence of hyperandrogenism. However, many believe that the occurrence of hyperandrogenism is a must criterion for PCOS that plays an important role in the pathophysiology of PCOS. Biochemically, hyperandrogenism is defined as a high testosterone concentration as well as other calculated parameters of androgen excess such as free testosterone (FT) and free androgen index (FAI). Hyperandrogenism in women with PCOS manifests clinically as hirsutism, acne, and androgenic alopecia. Other indications of elevated androgen excess include weight gain, menstrual abnormalities, acanthosis nigricans, and insulin resistance. **(5).**

Hirsutism is the appearance of terminal hair on the face and/or body in a masculine pattern. It is one of the most common symptoms of PCOS hyperandrogenism. In PCOS women, the prevalence of hirsutism ranges from 60 to 80%. The degree of hirsutism varies according on the population's ethnicity. Androgens, particularly testosterone, control the amount and distribution of hair growth. **(6).**

Ferriman and Gallwey described a visual scoring method to clinically assess the degree of hirsutism. According to the FG score, hair is scored in nine parts of the body, which include the upper lip, chin, chest, upper and lower back, upper and lower abdomen, and upper and lower limbs. A score of 0–4 is given on these nine body parts to determine the extent of hirsutism, with a score of 0 representing a complete absence of terminal hair and a score

ISSN: 0975-3583, 0976-2833 VOL 12, ISSUE 04, 2021

of 4 represents extensive hair growth. Women with FG score of 8 or higher are regarded as hirsute. **(7)**

Acne vulgaris is the second most common symptom of hyperandrogenism. According to some studies, acne patients with PCOS account for 9.8 - 34% of all acne cases. The formation of the more potent form of dihydrotestosterone causes abnormal desquamation of the follicular epithelial cells and increases the production of sebum in the sebaceous glands. Propionibacterium acnes colonize the buildup of sebum and epithelial debris, causing acne. **(5).**

Alopecia Androgenic alopecia, also known as male pattern baldness, is another symptom of PCOS women's hyperandrogenic condition. Alopecia in PCOS appears to be frequent, with rates ranging from 3.2 to 34.8 % in various groups. PCOS women have high amounts of testosterone, which causes hair loss **(5).**

2. Obesity:

In fact, the risk of PCOS increases as one's weight rises. Obesity or overweight is common among PCOS women, with 30% to 75% of them being overweight or obese. Increased abdominal fat is seen in normal weight PCOS women as well, indicating that abdominal and visceral adipose tissue plays a major role in the development of this condition. Obesity has an important impact on the severity PCOS particularly in the presence of increased abdominal fat. The chance to conceive among obese women with PCOS is lower than that in those with normal weight. Furthermore, obese PCOS women require increase doses of ovulation-inducing drugs to achieve ovulation. The BMI of all infertile women with PCOS should be assessed because obesity is linked to anovulation. For PCOS women who are unable to conceive, weight loss and other lifestyle changes are the first-line therapy**. (4)**

3. Insulin Resistance:

Insulin resistance (IR) is defined as the inability of exogenous or endogenous insulin to increase glucose uptake and its utilization. Insulin resistance and hyperandrogenism play a key role in the pathophysiology of PCOS. In fact, insulin resistance is found in 85% of PCOS women (75% and 95% for non-obese and obese subjects, respectively). **(4)**

Insulin resistance and obesity are considered intrinsic to PCOS but neither of them is included in the guidelines and should therefore be used

For diagnostic purposes**. (8).**

Insulin resistance, compensatory hyperinsulinemia, and hyperandrogenism are all phenotypes that female patients with insulin receptor gene mutations have. Despite the fact that IR and hyperinsulinemia are frequent in PCOS patients, insulin receptor gene mutations are relatively rare. Women with PCOS have inherent IR, regardless of the degree of obesity or the size of androgen levels. Even thin women with PCOS develop IR, and a higher body mass index (BMI) worsens the condition. In comparison to normal-weight

ISSN: 0975-3583, 0976-2833 VOL 12, ISSUE 04, 2021

females, teenage girls with PCOS have peripheral IR, increased liver fat, and muscle mitochondrial dysfunction. ***(9).***

4. Endometrial Receptivity:

While anovulation is the most evident cause of infertility in women with PCOS, endometrial receptivity issues may also be a factor. The endometrium is subjected to unopposed oestrogen stimulation due to ovulatory disorder, resulting in an altered endometrial milieu. Women with PCOS do have a lower implantation rate and a higher rate of miscarriage, which has been linked to poor endometrial receptivity. Several studies have found that women with PCOS have a higher chance of miscarriage (up to 50%). ***(4)***

5. Oocytes and Embryo Quality:

Women with PCOS who receive regulated ovarian stimulation create a large number of follicles. However, poor oocyte quality has been recorded, resulting in low fertilisation and implantation rates as well as a greater miscarriage rate. This could be due to modifications in the intrafollicular microenvironment during folliculogenesis and follicle maturation, which could affect oocyte competence and embryonic development. It's linked to a lack of communication between cumulus cells and oocytes, as well as aberrant paracrine/endocrine factors and metabolic abnormalities. ***(4,*6).**

6. ***Vitamin D:***

Vitamin D deficiency was shown to be common in PCOS women (67–85 % against 20–48 % in the general population). Vitamin D levels are linked to hormonal disruption and metabolic state in women with PCOS. Insulin resistance and metabolic syndrome may both be exacerbated by vitamin D deficiency and Obesity, by trapping the lipophilic vitamin in the adipose tissue. There has also been evidence of a link between vitamin D insufficiency and infertility. Low levels of vitamin D in the follicular fluid have been linked to reduced implantation and live birth rates in recent research. **(10).**

❖ ***Long term consequences of PCOS***

1. **Gestational diabetes, and type 2 diabetes*:***

Gestational diabetes and type 2 diabetes General guidelines recommend. All adults with PCOS and adolescents with extra risk factors (age >40, BIM>25kg/m2, family history, Hypertension, High risk ethnicity) should be screened, according to the GDM. Fasting glucose, HbA1c, or OGTT can be utilised as alternatives to the optimal testing. A75-g OGTT should be offered in all women with PCOS preconception when planning pregnancy or seeking fertility treatment, given the high risk of hyperglycaemia and the associated comorbidities in pregnancy. If not performed preconception, an OGTT should be offered at < 20 weeks gestation, and all women with PCOS should be offered the test at 24-28 weeks gestation. Frequency of testing should be a minimum of three yearly informed by additional risk factors. **(11).**

ISSN: 0975-3583, 0976-2833 VOL 12, ISSUE 04, 2021

2. Menopause life stage:

Postmenopausal persistence of PCOS should be considered a possibility if indications of hyperandrogenism remain. If there is a past diagnosis of PCOS, along- term history of irregular menstrual cycles, hyperandrogenism, and/or PCOM during the reproductive years, a diagnosis of PCOS post menopause could be explored. **(12) .**

3. Cardiovascular disease:

Women with PCOS have an increased prevalence of coronary artery calcification and thickened carotid intima media, which may be responsible for subclinical atherosclerosis. Prospective, long-term cardiovascular-outcome studies in PCOS are needed to assess whether the increased cardiovascular risk in PCOS results in the higher cardiovascular-event rates. ***(13).***

4. Endometrial hyperplasia, carcinoma:

Associations between PCOS and endometrial cancer are complex.

Women with PCOS appear to have an increased risk of endometrial cancer consistent with anovulation and increased prevalence of obesity. Routine screening for endometrial cancer in PCOS is not recommended, however vigilance and awareness of increased risk is important. **(12) .**

5. Breast cancer:

Obesity, hyperandrogenism and infertility are features known to be associated with the development of breast cancer. However, studies failed to show any significant increase in the risk of developing breast cancer in women with PCOS. **(11).**

6.* Ovarian cancer*:

There has been much debate and concerns about the risk of ovarian cancer in women with anovulation, particularly because of the extend use of drugs for induction of ovulation to these patients. Several lines of evidence might suggest that there is a connection between PCOS and increased risk of ovarian cancer. **(14).**

7. Obstructive sleep apnea (OSA):

It appears more common in PCOS and obesity. The prevalence of OSA in the adult population generally varies across cohorts and ranges from 9 -38%. Androgen levels and insulin resistsnce are positively with Obstructive sleep apnea in PCOS. **(12) .**

❖ ***Management of Polycystic Ovary Syndrome***

I. **Lifestyle changes:**

- **Lifestyle changes:** promoting weight loss, are the first-line treatment recommended for women with PCOS. A good diet and regular physical activity are known to aid in the reduction of IR and hyperandrogenism, as well as the optimization of hormonal imbalance, lipid profile, and cardiovascular health. According to one study, losing just 5% of one's baseline body weight can restore normal menses and increase sensitivity to ovulation-inducing and reproductive medicines. ***(3,11).*** The reduced glycemic load by reducing sugar content and more complex carbohydrates, avoid fatty meals plus thirty minutes per day of brisk exercise is advised to maintain health ***(15).*** The British Fertility Society guidance suggests that treatment should be deferred until BMI less than 35Kg/m2***. (16).***
- ***Bariatric surgery*** is the most effective way for weight loss. It attenuates PCOS's associated clinical symptomatology, such as menstrual irregularity, hirsutism, and, possibly infertility. In patients trying to conceive after bariatric surgery, one meta-analysis reported up to 58% spontaneous conception rates, bariatric surgery could be considered in women with PCOS, who have a BMI ≥ 35 kg/m, and who remain infertile. ***(3).***

II. Pharmacological treatment for non-fertility indications:

1. Combined contraceptives*:*

First-line medical therapy usually consists of an oral contraceptive to induce regular menses. The COC not only inhibits ovarian androgen production but also increases sex hormone-binding globulin, decreasing androgen bioavailability, COC reduce terminal hair growth, although many patients still require concomitant mechanical hair removal. **(17).**
The effects of COCPs on menstrual cycle, hirsutism, weight loss, waist/hip ratio, testosterone concentrations, lipid profile and blood sugar levels are variably reported and depend on type of COCP used, duration of use. COCPs come in a variety of combinations, as well as oestrogen and progestin formulations with different pharmacological and clinical effects. **(12) .**

The progestin, present in oral contraceptives, has a protective effect on the endometrium. It has been proven that decrease the risk of endometrial cancer. ***(18).***

2. Metformin:

Metformin is a low-cost, generally available medicine that has been widely utilised as an insulin sensitizer in DM2 and PCOS for over seven decades. Insulin resistance has been shown in 75% of lean women and 95% of overweight women in clamp studies, and addressing this has been the driving force behind the use of metformin in PCOS **(12) .**

3. . Anti-androgen pharmacological agents:

Hirsutism, acne, and androgen-related alopecia are the most prevalent androgen-related symptoms of PCOS. Cosmetic and COCP therapy are the first-line therapies for female hirsutism, including PCOS. There are few studies on the use of anti-androgen pharmacological drugs in the treatment of PCOS. **(6).**

4. Inositol:

Inositol (myo-inositol and di-chiro inositol) is a nutritional supplement that acts as a second messenger and has been shown to play a role in insulin signaling transduction. Previous studies have focused on insulin resistance and hormonal profiles and gestational diabetes in women with PCOS. Currently, given the lack of evidence, international guidelines recommend that inositol should be considered an experimental therapy in PCOS. **(6).**

III. Assessment and treatment of infertility

1. Drug Therapy for anovulation:

❖ ***Letrozole***

An alternative first line therapy to stimulate ovulation could be letrozole ***(15).*** Aromatase inhibitors (AI) are effective as ovulation-inducing agents, including letrozole and anastrozole, with letrozole being the most widely used**. (6).**

Letrozole inhibit aromatase enzyme which decrease the aromatization of androgens to estrogens that in turn release the hypo thalamic pituitary axis from negative feedback of estrogen. Adverse effects on the endometrium and cervical mucus are less than with Clomiphene citrate (CC) and reports a good pregnancy rate. ***(3).***

❖ ***Clomiphene citrate***

Clomiphene citrate (CC) is a selective oestrogen receptor modulator with both oestrogenic and anti-oestrogenic properties. It was first approved for use in women with anovulation in 1967 and acts as an anti-oestrogen. Due to the anti-oestrogenic effects of CC on the endometrium and cervical mucus, there is a contradiction between good ovulation rates and reduced pregnancy rates. The chances of having twins or triplets with CC are 5–7% and 0.3 0%, respectively, whereas the chance of having OHSS is less than 1%. With 12 cycles or more, there is a slight increase in the risk of ovarian tumors. **(6).**

Current evidence-based guidelines propose the use of CC, as a second-line therapy, in women with PCOS with anovulatory infertility and no other infertility factors to improve ovulation and pregnancy rates**. *(3).***

❖ ***Gonadotrophins***

Gonadotrophin therapy is suitable for improving infertility in women with PCOS in specialist care. Gonadotropin therapy provides better per cycle and cumulative pregnancy and live birth rates compared with the use of oral anti-oestrogens and or no therapy in anovulatory women with PCOS; and there is no evidence of teratogenicity. It is important to note that gonadotrophin therapy requires daily injections and the need for intensive monitoring with ultrasound; with a risk of multiple pregnancy and increased cost of medication compared with oral agents. **(12) .**

In PCOS patients, gonadotropins are associated with a higher risk of OHSS and multiple pregnancies so they should only be used by clinicians having the requisite training and experience To prevent hyperstimulation and minimize multifollicular development, low-dose step-up or a step- down protocols are preferred .In the low-dose step-up protocol, low initial doses of gonadotropins are used, after a menses, starting with 37.5 to 75 IU/d, and increasing in small increments 25 to 37.5 IU after 7 days or more if no follicle >10 mm has developed. Ultrasonography provides measurement of follicular development and generally should be performed after the first 4 to 5 days of treatment and at subsequent intervals of 1 to 3 days according to response. Although 7 to 12 total days of treatment is typical, longer durations of treatment may be required. **(19).**

2. *Laparoscopic ovarian drilling:*

In last years, the rapidly expanding field of operative laparoscopy has led to a renewed interest for surgical treatment for PCOS. Several methods of laparoscopic treatment have been studied, including biopsy, electro-cautery and laser treatment. ***(20).***

For women with anovulatory infertility who are resistant to pharmacological treatment, a minimally invasive surgical approach, laparoscopic ovarian drilling (LOD), may be an option for ovulation induction. ***(21).***

3. *Vitamin D:*

The prevalence of vitamin D insufficiency or deficiency in reproductive age women is 45% to 90%. PCOS and vitamin D deficiency are both associated with IR. A study found that vitamin D deficiency in women with PCOS who underwent ovarian stimulation for the treatment of infertility was associated with significantly diminished rates of ovulation, of pregnancy, and ultimately a reduced chance of live birth***. (10).*** Vitamin D supplementation may be recommended as a potential therapeutic adjunct for the ovulatory dysfunction and metabolic disorders observed in women with PCOS**. (12) .**

4. Assisted reproductive technologies (ART):

ART, mainly in vitro fertilization (IVF), intracytoplasmic sperm injection (ICSI) and in vitro maturation (IVM), have a role in PCOS after failure to respond to pharmacological

ovulation induction or if there are other indications such as tubal damage or male factor infertility. **(12) .**

Women with anovulatory infertility secondary to PCOS should first be treated by ovulation induction and only then proceed to IVF if a pregnancy does not result despite repeated ovulation. IVF is considered as the third-line management for PCOS. when first- and second-line agents have not been successful in achieving a pregnancy or when there are additional causes of infertility such as pathology of the fallopian tubes or sperm abnormalities in the woman's partner. The presence of polycystic ovaries is a major risk factor for developing ovarian hyperstimulation syndrome (OHSS) and so care is required when planning the stimulation regimen .**(22) .**

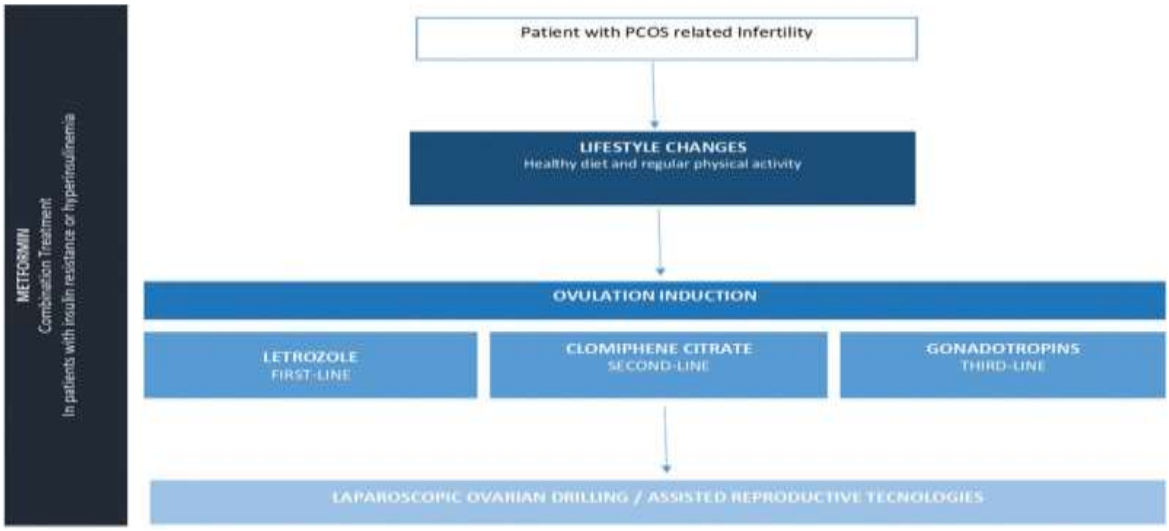

Figure 2; proposed management of polycystic ovary syndrome related infertility ***(3).***

The fact that ovarian hyperstimulation is not required means that In vitro maturation(IVM) is especially suited to patients with PCOS, who are at increased risk of exaggerated ovarian response, including OHSS, ovarian torsion, and thromboembolism associated with high estradiol levels In addition, because the reduced ability of immature oocytes retrieved from mid-antral follicles to resume meiosis and progress to the metaphase II stage is a limiting factor of the clinical efficiency of IVM the higher antral follicle count in women with PCOS makes them particularly suitable candidates for IVM. This is shown by higher IVM success rates in women with PCOS compared with normo-ovulatory women. **(23).**

References.

1. **Eldib, Abdallah and Osama A Tashani.** "Infertility in the Middle East and North Africa Region: A Systematic Review with Meta-Analysis of Prevalence Surveys. no. 2 (2018): 37-39.

2. **Ramezanali, Fariba, Mahnaz Ashrafi, Mandana Hemat, Arezoo Arabipoor, Samaneh Jalali and Ashraf Moini.** "Assisted Reproductive Outcomes in Women with Different Polycystic Ovary Syndrome Phenotypes: The Predictive Value of Anti-Müllerian Hormone." Reproductive biomedicine online 32, no. 5 (2016): 503-512.

3. **Cunha, Anita, and Ana Margarida Póvoa.** "Infertility Management in Women with Polycystic Ovary Syndrome: A Review." Porto Biomedical Journal 6, no. 1 (2021). 11-34.

4. **Palomba, Stefano**. Infertility in Women with Polycystic Ovary Syndrome: Pathogenesis and Management: Springer, (2018).1-9.

5. **Ashraf, Sairish, Mudasar Nabi, Fouzia Rashid and Shajrul Amin**. "Hyperandrogenism in Polycystic Ovarian Syndrome and Role of Cyp Gene Variants: A Review." Egyptian Journal of Medical Human Genetics. (2019): 1-10.

6. **Teede HJ, Miso ML, and Costello MF.** Recommendations from the international evidence-based guideline for the assessment and management of polycystic ovary syndrome. Clin Endocrinol (2018); 89:251-268.

7. **Coskun A, Ercan O, and Arikan DC.** Modified Ferriman-Gallwey hirsutism score and androgen levels in Turkish women. Obstet Gynecol Reprod Biol.; **(**2014) 154(2):1 67-71.

8. **Le MT, Nguyen VQH, Truong QV, Le DD, Sa Le VN, and Cao NT.** Metabolic Syndrome and Insulin Resistance Syndrome among Infertile Women with Polycystic Ovary Syndrome: A Cross-Sectional Study from Central Vietnam. (2018); 33(4):447-458.

9. **Witchel, Selma Feldman, Helena J. Teede and Alexia S Peña.** "Curtailing Pcos." Pediatric Research 87, no. 2 (2020): 353-361.

10. **Butts SF, Seifer DB, and Koelper N.** Vitamin D deficiency is associated with poor ovarian stimulation outcome in PCOS but not unexplained infertility. Endocrinol Metabolic. 2019; 104:369– 378.

11. **RCOG guidelines. (The Royal College of Obstetrics and Gynecology) (2018).** Rotterdam ESHRE/ASRM- Sponsored PCOS Consensus Worksho Group. Revised (2003) consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome. Fertil Steril. (2004); 81(1):19-25.

12. **ESHRE (European Society of Human Reproduction and Embryology).** Teede, H., Misso, M., Costello, M., Dokras, A., Laven, J., Moran, L., Piltonen, T., & Norman, R. International evidence-based guideline for the assessment and management of polycystic ovary syndrome 2018; 33 (9),p 602-618.

13. **Santos, Betânia Rodrigues, Sheila Bünecker Lecke and Poli Mara Spritzer.** "Genetic Variant in Vitamin D-Binding Protein Is Associated with Metabolic Syndrome and Lower 25-Hydroxyvitamin D Levels in Polycystic Ovary Syndrome: A Cross-Sectional Study. 12, no. 3 (2017): 173-695.

14. **Daniilidis, A and Konstantinos Dinas.** "Long Term Health Consequences of Polycystic Ovarian Syndrome: A Review Analysis." Hippokratia 13, no. 2 (2009): 90-99.

15. **Legro R , Richard S, and Silva S.** Ovulation induction in polycystic ovary syndrome: current options. Best Pract Res Clin Obstet Gynaecol. (2016); 37:152–159.

16. **Balen, Manuela, Gabriela Rotta Gomes, Jadel M Kratz, Cláudia MO Simões, Alexsandra Valério and Débora de Oliveira.** "Enzymatic Synthesis of Ascorbyl Ester Derived from Linoleic Acid." Bioprocess and biosystems engineering 40, no. 2 (2017): 265-270.

17. **Goodman NF, Cobin RH, and Futterweit W.** American Association of Clinical Endocrinologists, American College of Endocrinology, and Androgen Excess and PCOS Society disease state clinical review: guide to the best practices in the evaluation and treatment of polycystic ovary syndrome - part 1. Endocr Pract.(2015); 21: 1291-300.

18. **Wiegratz I. and Kuhl L.** Long-cycle treatment with oral contraceptives. Drugs; (2004): 64:447-62.

19. **Weiss NS, Kostova E, Nahuis M, Mol BWJ, van der Veen F,and van Wely M**. Gonadotrophins for ovulation induction in women with polycystic ovary syndrome. Cochrane Database Syst Rev. (2019);1-23.

20. **Yanamandra NK and Gundabattula SR.** Outcome of ovarian drilling in women with polycystic ovary syndrome. J Clin Diagn Res; (2015): 9(2):1-3.

21. **Neven ACH, Laven J, Teede HJ, and Boyle JA.** A summary on polycystic ovary syndrome: diagnostic criteria, prevalence, clinical manifestations, and management according to the latest international guidelines. Semin Reprod Med. (2018); 36:5–12.

22. **Khaldoun Sharif MBBCh (Hons), MD, MFFP, FRCOG, FACOG, Arri Coomarasamy MBChB, MD, FRCOG, Fm..** Assisted_Reproduction_Techniques_Challenges_and_Manageme(2021) p.78-92.

23. **Vuong, L. N., Ho, T. M., Gilchrist, R. B,and Smitz, J.** The Place of In Vitro Maturation in Assisted Reproductive Technology. Fertility & Reproduction, (2019). 01(01), 11–15.