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Research article

An update of polycystic ovary syndrome: causes and therapeutics options

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ABSTRACT

Polycystic ovary syndrome (PCOS) is a heterogeneous disorder characterized by menstrual irregularities, chronic anovulation, hirsutism, androgenic alopecia, and acne. At diagnosis, patients can with different manifestations according to the disease phenotype, patient's age, and lifestyle. However, most patients pursue medical care because of the clinical symptoms of PCOS, such as hyperandrogenism, menstrual irregularities and infertility. Recent studies have shown that PCOS is associated with 80% of anovulatory infertility; however, the precise mechanism of PCOS-induced anovulation is still undetermined. The treatment strategies of PCOS are symptomatic depending mainly on the desired goals and clinical benefits. Life style intervention is still the first line treatment option for overweight females seeking pregnancy. In addition, there are many pharmacological agents that could be added to induce ovulation such as metformin, and clomiphene citrate. Nowadays, many patients preferred to use some herbal medicine that was proved to have potential therapeutic benefits in many studies in the management of PCOS. The purpose of this review was to discuss PCOS-induced infertility and the available therapeutic options as well as the impact of COVID-19 infection on the success of fertility attempts. To address this purpose, Pubmed, Scopus, EMBASE and Google databases were searched for studies discussing PCOS-induced infertility. The literature search revealed the proper therapeutic plans to treat PCOS-induced infertility, and that treatment should be modified according to patient's complaints, reproductive desires, and disease phenotypes. In conclusion, the use of specific therapeutic agents and patients' adherence to lifestyle interventions could help patients recover their reproductive and metabolic health.

1. Introduction

Polycystic ovary syndrome (PCOS) is the most common chronic reproductive and metabolic endocrine disorder affecting women of childbearing age, with prevalence estimated to be 4%–21% worldwide [1, 2]. It was first described by Hippocrates in 377–460 BC as "women whose menstruation is less than 3 days or meager are robust, with a healthy complexion and a masculine appearance; yet they are not concerned about bearing children nor do they become pregnant" [3].

Polycystic ovary syndrome is a heterogeneous disorder characterized by a triad of hyperandrogenism, menstrual irregularities and polycystic ovaries. Therefore, patients can present with different manifestations of this triad depending on the disease phenotype, patient's age, and lifestyle [5]. However, most patients seek medical care because of the clinical symptoms of hyperandrogenism, menstrual irregularities and infertility [6].

Clinical signs of hyperandrogenism that are frequently seen in PCOS are hirsutism, androgenic alopecia, and acne [7]. A recent study showed that more than 80% of females with symptoms of hyperandrogenism are diagnosed with PCOS [6]. Additionally, 70–80% of females with PCOS complain of male-like pattern hirsutism of terminal hir grown on the lower face, chin, and neck [5, 8, 9]. In addition to hirsutism, women with PCOS may present with alopecia. A retrospective cohort study showed that 22.4% of females with PCOS who were attending the PCOS multidisciplinary clinic in San Francisco (USA) had androgenic alopecia [10]. Acne is another clinical sign of hyperandrogenism but it is less prevalent and specific than hirsutism [6]. Approximately 15%–25% of females with PCOS present with acne [11]. The increased androgen levels in PCOS stimulates sebum production in the sebaceous gland [12] which can lead to moderate to severe acne [13].

Patients with PCOS may complain of oligomenorrhea, secondary amenorrhea or dysfunctional uterine bleeding [14]. Approximately, 85%–90% of females with oligomenorrhea and 30%–40% of females with amenorrhea have PCOS [5]. In addition to infertility, can lead to serious complications such as metabolic syndrome, diabetes mellitus, dyslipidemia, endometrial cancer and cardiovascular disease [3]. Due to

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these complications, PCOS is considered a metabolic reproductive syndrome [4]. Thus, women with PCOS should be diagnosed early, treated correctly and followed up carefully to avoid these detrimental effects.

The evolving field of personalized medicine is playing an increasingly important role in the clinical management of patients with PCOS. Identification of single nucleotide polymorphisms (SNPs) in relevant genes permits the use of screening genetic testing to predict the efficacy of various therapies and to avoid treatment-limiting toxicities [15, 16]. The aim of the present review is to describe PCOS as a multifaceted condition and to demonstrate the available therapeutic plan for the treatment of PCOS-induced infertility. In addition, the emerging evidence of the usefulness of personalized therapy and the related genetic basis are discussed in this review.

2. Methods

A comprehensive search was conducted using PUBMED, SCOPUS EMBASE and Google databases for studies discussing the PCOS-induced infertility managements in the last 11 years. Mesh headings included polycystic ovary syndrome (PCOS), PCOS-induced infertility, PCOS and/anovulatory infertility, hyperandrogenism, PCOS and menstrual irregularities, and infertility. Three authors (AR, BM, AY) conducted the search and independently screened eligible titles to obtain articles for full-text review. Abstracts were reviewed for all articles collected through the electronic search process. Articles unrelated to the main topic, duplicates, and conference abstracts were excluded from the review process. Only articles published in English were considered. The titles and abstracts of the retrieved articles were screened, after which the full text of potentially relevant articles were printed and read. Next, a reference search of these relevant articles was performed.

2.1. Pathophysiology of PCOS- induced infertility

Hirsutism and infertility are the principal reasons that cause a patient with PCOS to seek medical attention. Polycystic ovary syndrome accounts for 80% of anovulatory infertility [17, 18]. Generally, most patients with PCOS-induced anovulation have irregularities in their menstrual cycle, commonly amenorrhea or oligomenorrhea, combined with hyperandrogenism. The precise mechanism of PCOS-induced anovulation is undetermined; however, there is evidence to support the hypothesis that early maturation of some follicles in polycystic ovaries lead to arrested antral follicle growth [19, 20]. Anovulation in PCOS is characterized by the inability of assortment of the dominant follicles in granulosa cells which causes arrest of follicle advancement [20]. This will cause an increase in estradiol (and progesterone) production that could suppress the endogenous follicular stimulating hormone (FSH). Gorry et al. suggested that the environment of granulosa cells in PCOS females could lead to an anomalous interface between insulin and luteinizing hormone (LH) [19]. They justified their theory with evidence showing that the increase in LH secretion relates to hyperinsulinemia, which is characteristic of the anovulatory female with PCOS [19, 21]. In addition, women with PCOS were found to be more prone to metabolic disorders such as diabetes mellitus and dyslipidemia compared to women without PCOS [22, 23]. The prevalence of glucose intolerance and diabetes mellitus were reported to be 23%–35% and 4%–10%, respectively [24]. Conversely, it had been shown previously *in vitro* that the granulosa cells' steroidogenic effect to LH is mainly increased by the accumulation of insulin [19], suggesting that insulin is a key determinant in arresting the antral follicles growth.

Anti-Müllerian hormone or Müllerian-inhibiting hormone (AMH or MIH) is a glycoprotein hormone released from the granulosa cells of preantral and small antral follicles in women. In addition to its major role on the hypothalamic–pituitary–gonadal axis, AMH has an important function in both gonadal function and sexual differentiation [25]. AMH can serve as a molecular biomarker for PCOS and comparative size of the ovarian preserve. AMH receptors are expressed in the gonadotropin-releasing hormone (GnRH) neurons. Evidence from the literature showed that GnRH is disrupted in females with PCOS, and the serum levels of AMH were generally increased [26]. Consequently, the pathophysiology of infertility in women with PCOS could involve the disturbances of AMH-dependent regulation of GnRH release.

Obesity accounts for 90% of infertility cases of PCOS [3]. It is an independent factor of infertility and may cause many obstetric complications [27]. Adiposity (body mass index (BMI) > 30 kg/m^2) is correlated with anovulation, causing a higher risk for infertility due to increase in the androgen concentration [28]. Weight reduction in obese females with PCOS leads to improving the menstrual cycle and fertility due to the reduction in circulating insulin and androgen levels.

2.2. Diagnosis of polycystic ovary syndrome and infertility

There are three valid diagnostic criteria for PCOS. The first diagnostic criteria was established by the National Institute of Health (NIH) in 1990. This criteria was broadened in 2003 to involve additional clinical features and is referred to as the Rotterdam criteria. Finally, the Androgen Excess and Polycystic Ovary Syndrome Society (AE-PCOS) developed a new set of diagnostic criteria in 2006 [5,29]. However, the Rotterdam criteria remains the most used among physicians of various specialties [30].

The diagnosis of PCOS using Rotterdam criteria requires having two out of the following three findings: clinical/biochemical hyperandrogenism, oligo/amenorrhea and the appearance of polycystic ovary [31]. Clinical features of hyperandrogenism are acne, hirsutism or androgenic alopecia while biochemical changes involve high total, free or bioavailable testosterone level [9]. Oligomenorrhea is defined as having menstrual periods with an interval of more than 35 days or five to nine menstrual cycles per a year [32]. Amenorrhea is defined by a lack of menses for three or more consecutive months [33]. Polycystic ovary morphology is determined using ultrasound by the appearance of 20 or more follicles (2–9 mm in diameter) per ovary and/or ovarian volume is greater than 10 ml [34].

In addition, the diagnosis of PCOS is exclusionary which means that physicians have to rule out other common diseases that share similar clinical, biochemical, and morphological presentations. This includes thyroid disorders, hyperprolactinemia, and non-classis congenital adrenal hyperplasia [35]. For example, patients with primary hypothyroidism could present with irregular menses, infertility, and excess weight. A mild increase in free and total testosterone, free and total estradiol, prolactin, and LH may be found in the laboratory tests of these patients. Furthermore, ovarian morphological changes like bilateral multicystic appearance can be seen frequently on ultrasound [36].

According to the Rotterdam criteria, there are four PCOS phenotypes (Table 1). The classic phenotype includes the presence of both hyperandrogenism and ovulatory dysfunction with (A) or without (B) polycystic ovary morphology. However, females who ovulate normally have "ovulatory phenotype" (C). The "non-hyperandrogenic phenotype" is the fourth type in which ovulatory dysfunction presents with polycystic ovaries without overt hyperandrogenism [37].

Infertility is defined as a couple's inability to conceive after 12 months of regular unprotected sexual intercourse due to abnormal reproductive capacity [38]. It is often interchangeable with subfertility

Table 1. The four phenotypes of polycystic ovary syndrome.

	Clinical/ biochemical hyperandrogenism	Ovulatory dysfunction	Polycystic ovaries
Phenotype A	✓	✓	✓
Phenotype B	✓	✓	—
Phenotype C	✓	—	✓
Phenotype D	—	✓	✓

[39]. The most common cause of female infertility is ovulatory dysfunction [40]. Polycystic ovary syndrome is considered the most frequent contributory factor of anovulation among females with infertility risk approximated to be 15-fold higher in females diagnosed with this syndrome [11, 41]. Females having PCOS often complain of oligoovulation or anovulation so there will be no ready mature egg every month to be fertilized [41]. In addition, they are more likely to develop complications such as preeclampsia, preterm labor and gestational diabetes which are associated with reproductive failure [42].

Infertile women with PCOS should undergo an infertility workup that includes medical history, physical examinations, imaging and laboratory tests to exclude other causes of infertility [43]. The most important laboratory workup is presented in Table 2.

2.3. Management of PCOS- induced infertility

Infertility is the main reason for most ob/gnecology clinic visits by females complaining of PCOS. Fortunately, with the advancing scientific evidence-based therapeutic approach, there are many successful non-pharmacological and pharmacological treatments of PCOS-induced infertility. The main intent of these treatment strategies is ovulation induction. In the current review, we will discuss the role of lifestyle modifications, medications, herbal medicine, and assissted reproductive techniques in the management of PCOS-induced infertility.

2.4. Lifestyle modifications

Weight loss is considered the first line treatment for obese females with PCOS seeking pregnancy [44, 45, 46]. Weight loss through lifestyle interventions is considered the first line treatment for all overweight or obese female (BMI >25 kg/m^2) with PCOS [1, 17]. Conversely, preventing weight gain is necessary for lean women (BMI<25 kg/m^2). Several studies have shown that weight reduction of at least 5–10% of the total body weight can improve metabolic, psychological as well as reproductive disturbances associated with PCOS [47, 48]. These results have been associated with decreased insulin insensitivity, reduction of androgen levels, and restoration of ovulation [49].

Lifestyle modifications should involve eating a healthy hypocaloric diet (1200–1400 kcal/day) and engaging in regular physical exercise for at least 120 min/day for 3–5 days/week [44]. Patients should be encouraged to decrease the consumption of saturated fats and refined carbohydrates while increasing protein rich foods to promote satiety and improve insulin sensitivity [50]. It was found that diets rich in saturated fatty acids promotes lipopolysaccharide-mediated inflammation by increasing serum levels of tumor necrosis factor-alpha (TNF-α) and peripheral leukocytic suppression of cytokine-3 (SOCS-3) expression [51]. A low glycemic diet has the ability to reduce insulin resistance, fasting insulin, total cholesterol, low density lipoprotein (LDL), androgen level, and waist circumference (WC) in PCOS females when compared to high glycemic diet [52]. Additionally, a recent systematic review showed significant improvement in BMI, WC, fasting insulin, and insulin resistance in females with PCOS after vigorous exercise [53]. Furthermore, lifestyle modifications are associated with a significant improvement in the reproductive abnormalities associated with PCOS. A randomized clinical trial conducted at Penn State University between October 2008 and March 2014 on infertile females with PCOS who visited the Academic Health Centre compared the efficacy of preconception lifestyle intervention, combined oral contraception (OCP) and the combined treatment strategies on both reproductive and metabolic abnormalities. It was shown that weight loss through lifestyle changes was associated with higher ovulation ($P < 0.05$) and live birth rates ($P = 0.13$) compared to OCP [3].

The mental health of women with PCOS is also a very important issue because they are more susceptible to depression and anxiety. Sleep disorders play a role in the etiology and the development of mental health problem in these females [54]. Moreover, not getting enough sleep can cause metabolic and endocrine changes such as decreased glucose tolerance, decreased insulin sensitivity, increased evening concentrations of cortisol, decreased levels of leptin and increased hunger and appetite [55]. Therefore, it is recommended to refer patients who are suffering from sleep disturbances to a physician who are specialize in the diagnosis and the treatment of sleep disorders [56]. The results of studies that focused on lifestyle management are very promising and proved that this strategy has a significant impact on the disease course while being cost-effective. Physicians should encourage those who are suffering from PCOS to start making positive changes in their daily lifestyle to enhance and maintain weight loss as well as to prevent weight gain.

Table 2. Summary of the most common laboratory tests ordered for infertile females.

Laboratory Tests
Follicular stimulating hormone (FSH)
Leutinizing hormone (LH)
Estradiol
Progesterone
Testosterone
Sex hormone binding globulin
Prolactin
Thyroid stimulating hormone (TSH)
Antimüllerian hormone (AMH)

2.5. Ovulation induction medications

2.5.1. Clomiphene citrate

Clomiphene citrate (CC) is a selective estrogen receptor modulator and the most commonly used drug to induce ovulation in female with polycystic ovary syndrome [57]. Clinically, it competitively antagonizes the estrogen receptor in the hypothalamus to increase the release of gonadotropin releasing hormone [43]. Higher GnRH results in a higher production and secretion of FSH from the pituitary gland which stimulates follicles growth and recruitment [43]. The recommended initial dose of CC is 50 mg/day orally started about the 2nd to the 5th day of menstrual cycle for 5 days [58]. Ovulation often happens 5–10 days after the end of the treatment. The dose can be increased by 50 mg/day if ovulation doesn't occur in the previous cycle [58].

Approximately, 80% of females ovulate after CC treatment [49]. The effects of CC were compared to placebo in three randomized clinical trials in anovulatory women and the results were summarized in a meta-analysis. This meta analysis showed higher clinical pregnancy rate in all CC treated groups in comparison with placebo [59]. However, the long half-life of this drug, approximately two weeks, results in long-lasting side effects on endometrial development and cervical mucus [60]. In addition, it was estimated that 15%–20% of females with PCOS are resistant to CC and don't respond to a dose up to 150 mg/day for 5 days up to at least three treatment courses [46, 61]. However, the presence of such factors did not affect the use of CC as a first attempt of conception. Furthermore, there are still many recommendations from gynecologists to use CC as a first line treatment of anovulatory infertility in PCOS patients when no other infertility factors exist as it results in a high ovulation percentage if administered correctly.

2.5.2. Letrozole

Letrozole is an aromatase inhibitor drug that works by reversibly inhibiting the aromatization of androgens into estrogen. As a result, this increases FSH secretion from pituitary gland by inhibiting the negative feedback loop of estrogen on the hypothalamus [62]. Letrozole is given in a dose range of 2.5–7.5 mg/day starting around the third to seventh day of the menstrual cycle for five days [63, 64]. Currently, letrozole is preferred over CC for ovulation induction for two main reasons. First, letrozole has a higher ovulation rate (61.7% vs. 48.3%) and live birth rate

(27.5% vs. 19.1%) compared to CC in infertile women with PCOS [65]. Secondly, letrozole is associated with fewer side effects because of its higher elimination rate and short half-life [66]. However, it is being used off label as it has not been approved for infertility treatment by the Food and Drug Administration yet. Despite this disadvantage, letrozole should still be considered because of its advantages over other medications and is an important alternative in the case of CC resistance.

2.5.3. Metformin

Metformin is the most widely used insulin sensitizer agent in the management of PCOS. In addition to improving insulin sensitivity, metformin reduces androgen levels by decreasing androgen and LH secretion from the ovaries and pituitary respectively and increasing sex hormone-binding globulin (SHBG) production in the liver [49, 67]. Several clinical trials demonstrated significantly higher ovulation rates with metformin compared to placebo in females with PCOS [68, 69, 70]. Additionally, a meta-analysis of randomized placebo-controlled trials reported an improvement in the clinical pregnancy rates and the live birth rates among females taking metformin [71]. Furthermore, compared to clomiphene citrate (CC) alone the addition of metformin to CC was associated with higher clinical pregnancy and ovulation rates [72].

The usual metformin dose used for ovulation induction is 1500–2500 mg/day divided between two to three doses [62]. The most common side effects of metformin are nausea, abdominal pain, diarrhea and flatulence, which are associated with limited consequent compliance [73]. These side effects can be prevented by prescribing extended-release tablets or taking metformin with food [74]. The potential reproductive benefits of metformin has gained much interest in the last decades as its ability to improve insulin resistance blocks an important factor in the pathogenesis of PCOS. Furthermore, the addition of metformin to CC has been shown to be synergistic.

2.5.4. Gonadotrophins

Gonadotrophins are hormones endogenously produced by the pituitary gland and used as a second line agents to induce ovulation when there is no response to CC [75]. It acts by stimulating follicles growth and development in the ovaries [75]. Highly purified urinary-derived FSH, recombinent FSH and highly purified human menopausal gonadotrophin are the main gonadotrophins available on the market [76]. The most commonly encountered disadvantages of these agents are an increased risk of ovarian hyperstimulation syndrome and multiple pregnancies [77].

2.6. Single nucleotide polymorphisms in the treatment of PCOS

Pharmacogenomics is an important approach for improving medication selection, reducing adverse effects, improving patient compliance, and saving health care costs [78]. Although treatment with metformin is recommended as a first-line drug therapy to induce ovulation in patients with PCOS, it failed to achieve therapeutic goals in 20% of patients [79]. With the current level of evidence, PCOS patients may potentially benefit from genetic testing. For example, polymorphisms in the *STK11 (or LKB1)* and *OCT1* (organic cation transporter 1) genes have an impact on metformin pharmacodynamics and pharmacokinetics, respectively [80]. These polymorphisms may be useful for identifying metformin non-responders, who may benefit from an alternative treatment. Liver STK11 (or LKB1), also known as liver kinase B1 (LKB1), is a regulator of insulin sensitivity and glucose homeostasis [81]. In PCOS women, carriers of the G allele, heterozygous genotype (CG), a mutant genotype (GG) of *STK11* rs8111699 SNP, had a significant improvement in ovulatory frequency in comparison to those with the wild genotype (CC) [82]. Restoring ovulation is a key part of treating many patient complaints, including infertility, abnormal or no uterine bleeding, and reducing hyperandrogenic symptoms such as hirsutism, acne, and alopecia [83].

On the other hand, polymorphisms in the *OCT1* gene affect metformin pharmacokinetics. OCT1 mediates drugs transport in the liver [84]. Genetic variation in *OCT1* gene was linked to reduced hepatic uptake of metformin and may contribute to variation in response to the drug [15]. A previous study that included 87 PCOS and 113 control women analyzed the impact of *OCT1* rs683369 and rs628031 polymorphisms [85]. The results revealed that the SNP frequencies were not associated with the glucose tolerance test (OGTT) readings at baseline. However, PCOS patients with the G allele of OCT1 rs683369 and/or with the A allele of *OCT1* rs628031 had increased insulin sensitivity in comparison to those with the wild-type genotype after receiving treatment. Other candidate genes have recently been proposed in the literature, including *FSHR* (follicle-stimulating hormone receptor) [86], and *AR* androgen receptor [87]. Large prospective and randomized trials are needed: (i) to establish gene-based treatemnt guidelines; and (ii) to understand the interplay between different polymorphisms and other environmental/lifestyle factors [88, 89].

2.7. Herbal medicine as adjunctive therapy

Herbal medicine is one type of complementary and alternative medicine and its use by women has increased significantly in the last decade [90]. According to the literature, two out of five females with PCOS use herbal medicine to alleviate symptoms [91].

Cinnamon is a herbal remedy that is used widely in traditional health practice to regulate the menstrual cycle of patients with PCOS. This popular practice was supported by several clinical studies [90, 91, 92]. A dehydroepiandrosterone (DHEA)-induced PCOS mice model showed that the cinnamon treated group had restored cyclicity and ovarian morphology [93]. Improving metabolic risk factors is another beneficial effect of cinnamon use that was demonstrated in a double-blinded randomized controlled clinical trial [94]. This clinical study showed that cinnamon supplementation significantly reduced weight, fasting blood sugar (FBS), fasting insulin, total cholesterol, and LDL levels in females with PCOS compared to placebo [94]. Deecreased insulin resistance and increased high density lipoprotein (HDL) level were also reported [94].

Curcumin is one of the active ingredients found in the rhizome of tropical herb turmeric (Curcuma longa Linn) [95]. It is a food additive and coloring agent with a bright orange-yellow color [96]. Curcumin possesses various biological activities including antioxidant, anti-inflammatory, anti-microbial, anti-tumor, cardioprotective and neuroprotective effects involving multiple mechanisms [97]. This wide range of pharmacological activities promotes studying its potential effect in PCOS. A rat model of estradiol valerate-induced PCOS showed that PCOS groups treated with an intraperitoneal injection of curcumin had significantly lower levels of interleukin-6 (IL-6) and C-reactive protein (CRP) compared with untreated PCOS groups [98]. Additonally, a lower expression of TNF-α in the ovaries was observed [98]. Evidence of curcumin's antioxidant activity was also shown in sodium arsenite-induced ovarian oxidative injury in mice [99]. Curcumin was able to significantly decrease reactive oxygen species and malondialdehyde levels in ovaries as well as increase super oxide dismutase level [99]. Interestingly, curcumin can also decrease the serum insulin level and improve quantitative insulin sensitivity check index [100].

Marjoram is another herbal medicine that is traditionally used by females with PCOS to restore menstrual regularity. Although there are not enough studies that investigate the potential effect of marjoram, a clinical randomized controlled pilot study showed the ability of marjoram to reduce adrenal androgen level and improve insulin sensitivity [101]. In the DHEA-induced PCOS rat model, the marjoram treated group had significantly lower estradiol levels and improved insulin sensitivity [73]. Additionally, marjoram showed the ability to reduce ovary weight which suggests a reduction in the number of ovarian cysts [73]. Finally, there was evidence of anti-inflammatory and antioxidant effects of marjoram which would target the proposed pathogenetic mechanism of PCOS [73].

Thus, herbal medicine is a valuable option in the management of PCOS. Gynecologists have reported increased tendencies for the use this type of complementary medicine. This is mostly connected to the results

of previously mentioned studies that support the utility of these promising alternative medicines. Many of these herbs are effective on both the reproductive and the metabolic disturbances that accompany PCOS and have minimal side effects compared to the long term use of the conventional treatments [102].

2.8. Surgical management

Surgical interventios provide an alternative opportunity for patients who are unresposive to the conventional medical therapy. Laparoscopic ovarian drilling (LOD) [103] is a minimally invasive surgical approach that is used to treat PCOS-associated infertility after the failure of the medical options. In this procedure, perforations in the surface of the ovary and the stroma are done by either laparoscopic ovarian electrocautery (diathermy either by unipolar or bipolar) or laser vaporization using carbon dioxide (CO_2), argon, or neodymium-doped yttrium aluminum garnet crystal lasers [104]. LOD works by two proposed mechanisms: loosening the condensed cortical layers of the polycystic ovary and destroying the ovarian follicles and stroma that are responsible for androgen production which reduces plasma androgen levels and normalizes the hypothalamus pituitary axis [105].

In a clinical trial, fifty infertile PCOS females who are resistent to CC were included to study the effect of LOD on the hormonal profiles. Blood samples were taken to measure serum testosterone, LH, and FSH levels before and after LOD. The results showed that LOD significantly reduced testosterone, LH and the LH/FSH ratio [106]. Additionally, LH increases FSH and improves the rate of ovulation and clinical pregnancy [106]. This surgical approach has shown a lower risk of ovarian hyperstimulation syndrome (OHSS), multiple pregnancy, lower cycle cancellation rates in patients later submitted to IVF and, thus, fewer direct and indirect costs in comparison with medical therapy [107].

Bariatric surgery is a surgical procedure that is done to reduce body weight for obese females with PCOS. Obesity plays an important role in the pathogenesis of PCOS, therefore, weight loss through bariatric surgery could cause dramatic physical and hormonal changes in these patients [108]. Physicians usually reserve this procedure for females who did not respond to other interventions such as lifestyle modifications and traditional medications [109]. A cohort study conducted on 36 infertile women with PCOS and obesity after undergoing bariatric surgery evaluated them 6 months and one year after surgery. The results revealed a significant decrease in body mass index, free androgen index, free and total testosterone levels along with an increase in sex hormone binding globulin [110]. A reduction in the volume of the ovaries by ultrasound was also observed [110].

2.9. Assisted reproductive techniques

Artificial insemination and in-vitro fertilization (IVF) are the most popular types of assisted reproductive techniques. They are mainly used for infertile females with PCOS who are resistant to ovulation induction medication or when PCOS is accompanied by men's infertility factor or tubular damage [62]. In artificial insemination, a collected amount of sperm from the male will be inserted into the cervix or the uterus of the female around the ovulation time [111]. While in IVF, the ovaries will be stimulated to produce a large number of follicles, then oocyte retrieval will be done and then fertilized by a collected sperm of the male in a controlled environment in the laboratory [112]. Once embryos develop, they will be transferred to be implanted in the uterus.

The IVF success rate is estimated to be 50% in females younger than 35 years old [113]. However, it could be associated with a serious OHSS. OHSS manifests as ovarian enlargement, abdominal ascites and intravascular hemoconcentration due to the increased vascular permeability [114]. There are some suggested preventive strategies to reduce the risk of OHSS. These include concomitant use of aspirin during ovarian stimulation, the use of GnRH antagonist instead of GnRH agonist to prevent ovulation and avoid aggressive ovarian stimulation [115].

With the recent outbreak of coronavirus disease of 2019 (COVID-19), we cannot ignore its impact on all aspects of life. A question may cross the mind of couples who are planning for IVF: could COVID-19 infection affect the success of IVF cycle attempts? An observational study was conducted in a tertiary, university-affiliated medical center to assess the influence of COVID-19 infection on patient's performance during IVF. Patient's stimulation characteristics and embryological variables of subsequent IVF attempts before and after COVID-19 infection were compared [116]. This research demonstrated that the patient's performance and ovarian reserve were not affected in the immediate subsequent IVF cyle after recovering [116]. However, reduced proportion of top-quality embryos (TQE) was observed, therefore the authors suggested three months interval (time needed for folliculogenesis and spermatogenesis) before resuming the IVF cycle [116]. Another study investigated the changes on IVF cycle parameters and obstetric outcomes after COVID-19 exposure for both spouses. The result revealed that there were no significant differences in serum estradiol level, oocyte number, endometrial thickness, fertilization rate and number of TQE [117]. However, sperm concentration was markedly reduced [117]. The dissemination of COVID-19 vaccines and then considering it mandatory for all necessitated studies investigating the possible adverse effects of these vaccines on pregnant females especially for assisted reproductive techniques like IVF. Fortunately, COVID-19 mRNA vaccines are safe and were not shown to have a negative effect on reproductive potential [118]. According to a retrospective cohort study, this is because pregnancy outcome and the response to controlled ovarian stimulation were the same in vaccinated and unvaccinated females who undergone IVF [118].

Conversely, the treatment of many couples who were undergoing IVF was interrupted or postponed during COVID-19 quarantine. These couples were significantly psychologically affected. For that reason, fertility centres were advised to support their patients to remain psychological and physically fit to the next attempt [119].

3. Conclusion

In conclusion, the results of this narrative review discussed various studies dealing with the available treatment options for PCOS-induced infertility. Many successful non-pharmacological and pharmacological treatments have been developed to treat this problem. Although ovulation induction is still the main intent of these treatment strategies, patients' adherence to lifestyle interventions plays a major role in recovering their reproductive and metabolic health. For patients who did not respond to the first line agents, gonadotrophins are the proposed next step. Finally, assisted reproductive technique and LOD are alternative options for those who have failed ovulation induction therapy or have additional infertility factors. Bariatric surgery could be used to reduce body weight for obese females with PCOS when other solutions did not work. While there are many studies that explored the role of various herbal medicines in the management of this condition, further clinical studies are required to investigate the reproductive effect of herbs in PCOS-induced infertility.

Declarations

Author contribution statement

Abeer M Rababa'h and Bayan Matani: Conceived and designed the experiments; Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data; Wrote the paper.

Alaa Yehya: Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data; Wrote the paper.

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