Original Article

Current Pharmacotherapeutic Approach to the Management of Polycystic Ovary Syndrome

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Abstract

Purpose: Polycystic ovary syndrome (PCOS) is one of the most common causes of infertility and the treatment aims to correct the menstrual cycle, excess androgen characteristics such as hirsutism, acne, and alopecia and increase the pregnancy rates in patients who are planning to conceive. The objective of this review is to provide an overall view on the currently available treatment options for PCOS.

Methods: A comprehensive literature search was conducted in the database using MEDLINE, PUBMED, SCIENCE DIRECT, SPRINGER LINK, EMBASE, OVID and SCOPUS

Findings: The results of this review showed a wide range of therapeutic options that improves the overall life style of the PCOS patient. The proposed mechanism of PCOS include hypothalamic abnormal gonadotrophic releasing hormone pulsatile secretion, excess of luteinizing hormone, increased ovarian or adrenal androgen production, cortisol increased catabolism, and abnormalities in insulin production or action.

Implications: The current available therapeutic options include estrogen receptor modulators, insulin sensitizing agents, aromatase inhibitors, gonadotropins, combined oral contraceptives and anti-androgens which provides a successful improvement in the clinical presentation of the patient interfering with one or more mechanisms of PCOS.

Keywords: Polycystic ovaries; reproductive age; menstrual cycle; infertility; oligomenorrhea.

Introduction

Polycystic ovary syndrome (PCOS) is the most common multifactorial, heterogeneous and complex endocrine disorder among the women of reproductive age and affecting around 5-10% of the population [1-3]. Polycystic ovary (PCO) is more often defined as the presence of 12 or more follicles in each ovary measuring 2-9 mm in diameter and an increased ovarian volume (> 10 cm3). The upper limit of ovarian volume is 20 cm in premenopausal women and 10 cm in post-menopausal women [4]. Generally, PCOS is diagnostically characterized by chronic anovulation, oligomenorrhea/amenorrhea, infertility, polycystic ovaries under ultrasonography and clinical or biochemical hyperandrogenism [5]. Presently there are 3 criteria for diagnosis of PCOS. The NIH criterion [6] states that all three of the following parameters are required for a patient to diagnose PCOS: 1. Clinical or biochemical evidence of hyperandrogenism, 2. Oligo/anovulation, 3. Exclusion of other disorders causing PCOS symptoms. The second is Rotterdam criterion [7] which requires any 2 of the following features: 1. Oligo/anovulation, 2. Clinical/biochemical signs of hyperandrogenism/polycystic ovaries. The third criterion for diagnosis of PCOS is Androgen Excess Society [8] which states that three of the following are required for positive diagnosis of PCOS: 1. Clinical / biochemical evidence of hyperandrogenism, 2. Oligo/anovulation and polycystic ovarian morphology, 3. Exclusion of other androgen excess or related disorder. The most commonly used criterion for diagnosis of PCOS is Rotterdam criterion.

The drug treatment of PCOS is more clear and effective once etiology of PCOS is known. PCOS is reported to be multifaceted, polygenic, hormonal disorder and various mechanisms such as hypothalamic-pituitary-gonadal (HPG) axis, ovarian and adrenal androgen production, insulin action and gene regulating androgen and insulin biosynthetic pathway are known to influence the pathogenesis of PCOS [9]. Clinical presentation of PCOS shows oligomenorrhea and/or amenorrhea, reduced fertility, weight gain, hirsutism, alopecia, acne, depression and mood swings. These symptoms are attributed to chronic anovulation and excess androgen production. These above symptoms of PCOS can be minimized to certain extent by employing life style measures but therapeutic approach is necessary to reduce the risk of PCOS such as metabolic syndrome which includes cluster of medical conditions like obesity, elevated blood pressure, elevated glucose, high serum triglycerides and low density lipoproteins and

pregnancy complications. Moreover, life style modifications without any pharmacological treatment shows low success rate in ameliorating PCOS symptoms.

Currently, the therapeutic options of PCOS includes the usage of insulin sensitizing agents, aromatase inhibitors, estrogen receptor modulators, gonadotropins and hormonal therapy for abnormal levels of LH and FSH, anti-androgens and combined oral contraceptives pills (OCP) [10]. Aim of the treatment is to regulate the menstrual cycles, facilitating pregnancy by stimulating ovulation, reducing hirsutism and acne [11].

Insulin sensitizing agents which includes Biguanides, Thiazolidinediones, MyoInosiltol Bromocriptine and N-Acetyl Cysteine are drugs that alter metabolism thereby producing improvement in glucose and lipid profiles. They also ameliorate reproduction dysfunctions, regulate ovulation and menstrual cycle, increase the probability of conception and reduce androgen over-production as they are found to have direct effect on steroidogenesis [12]. Aromatase inhibitors such as Letrozoleare generally preferred as second line therapy and are used for anovulation where they induce ovulation without any anti-estrogenic effect. Estrogen receptor modulators such as Clomiphene Citrate induces ovulation by inhibiting the estrogen receptor. They also increase gonadotropin releasing hormone secretion, which induces rise in FSH and LH. They may have vasomotor symptoms and gastrointestinal disturbances. Antiandrogens such as Spironolactone, Finasteride and Flutamide are used for treating acne, hirsutism by blocking interaction of androgens with androgen receptor and also decrease the levels of testosterone. Oral contraceptive pills suppress production of ovarian androgen in order to regulate menstrual cycle, hirsutism and acne by direct negative feedback mechanism on LH secretion [13]. The vast majority of the women suffering from PCOS symptoms can be relieved by the rational use of available therapeutic options.

MATERIALS AND METHODS

The review was done after a thorough and comprehensive literature search in databases such as MEDLINE, PUBMED, SCIENCE DIRECT, SPRINGER LINK, EMBASE, OVID and SCOPUS. The search was conducted using key terms PCOS, reproductive age, treatment option, aromatase inhibitors, polycystic ovaries between 2005 and 2016. The search resulted in collection of 140 articles covering wide range of topics related to PCOS. The eligible literature articles in this review were narrowed down to original research articles and the language was restricted to English alone. The methods included in this review were prospective, retrospective, randomized, double blind, placebo controlled, cross sectional, observational, cohort study and open label studies. The articles that were excluded from this review were letter to the editors, animal model studies, opinion articles and case based learning articles. The data was extracted from each article after thorough reading about the treatment of PCOS. The data observed and recorded were year of publication, author, study design, patient's characteristics or sample size, treatment, efficacy of drug and outcome.

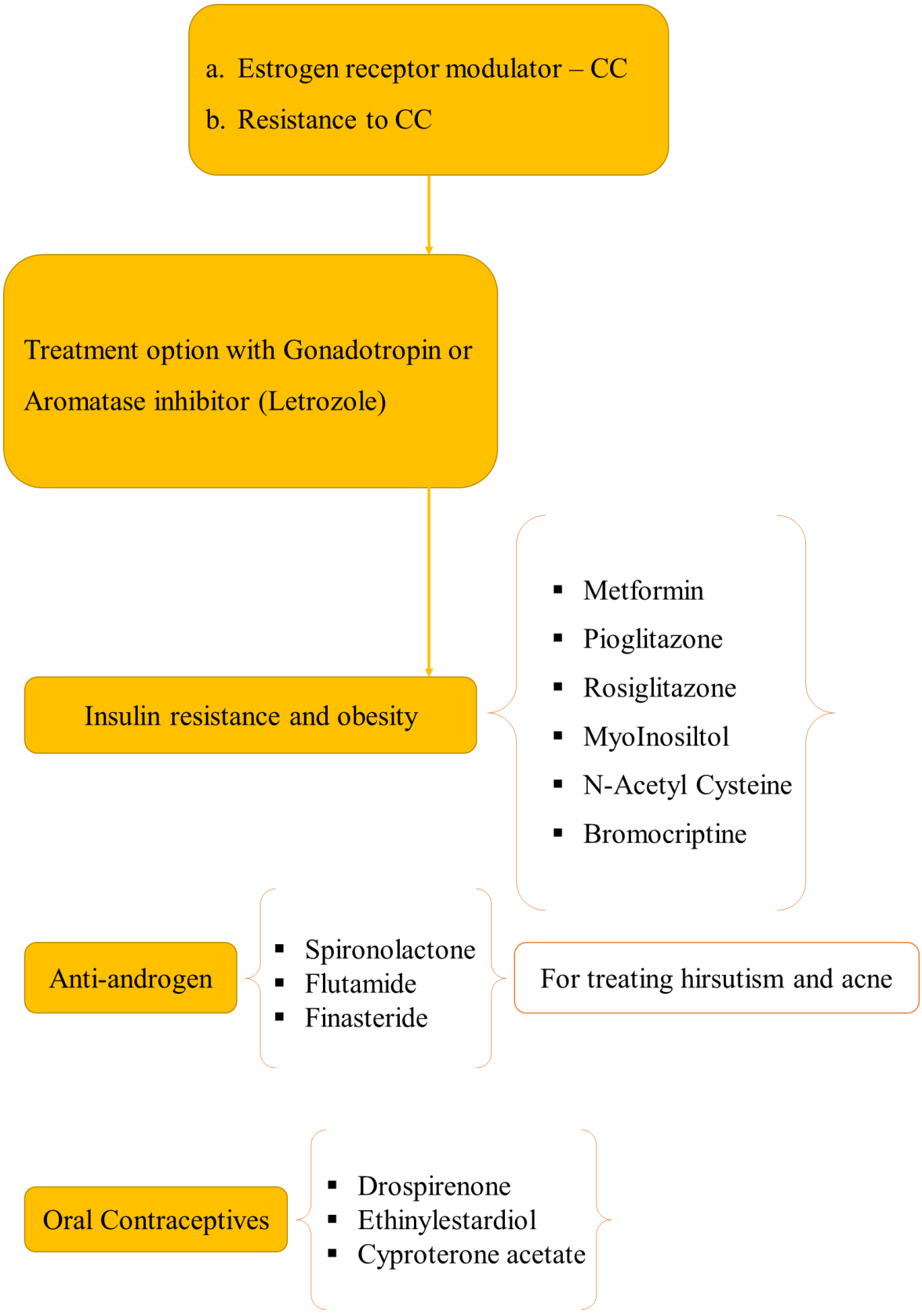

Fig. 1 Treatment options for PCOS

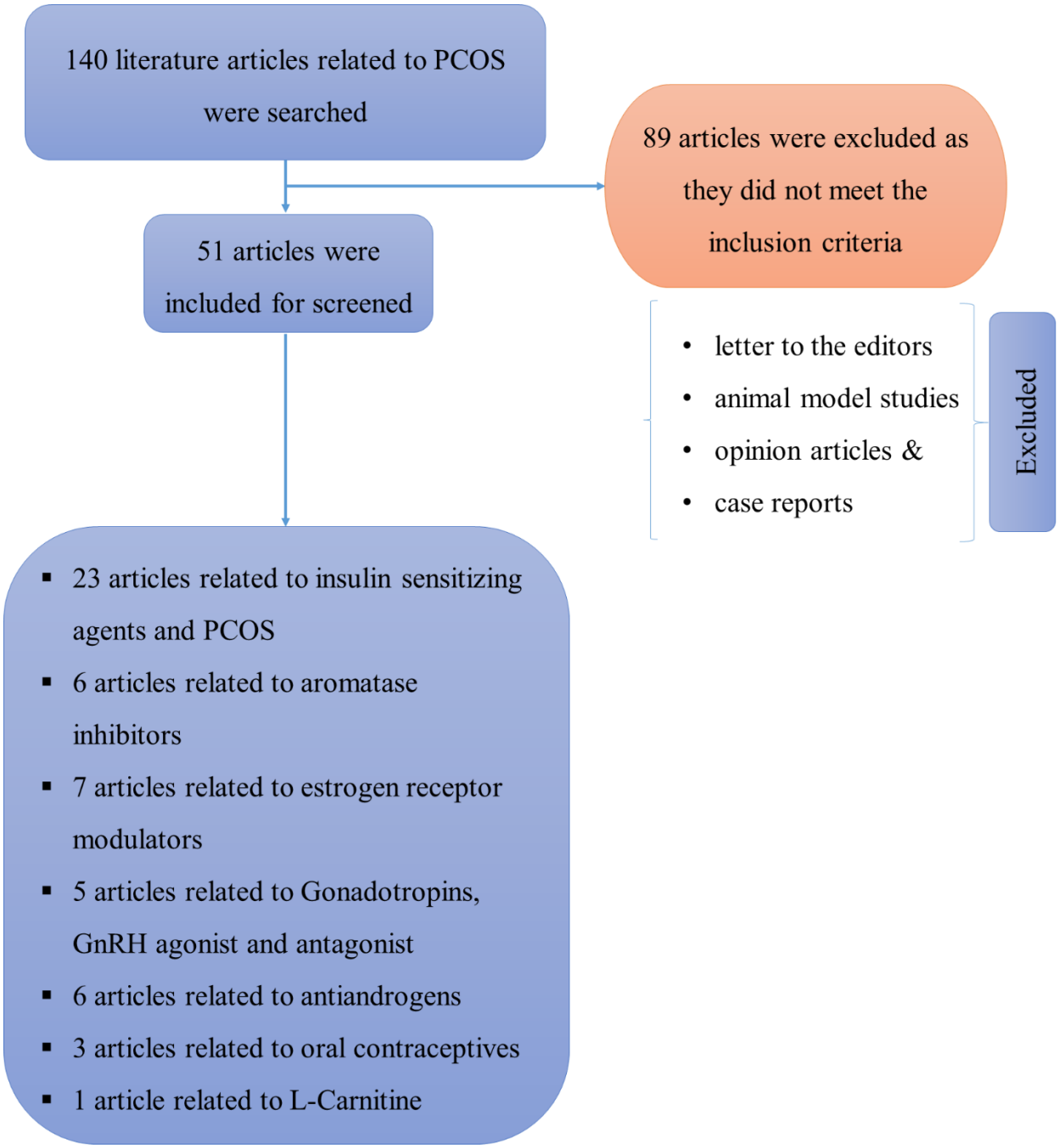

Fig. 2 Flow diagram of article search

RESULTS AND DISCUSSION

Insulin sensitizing agents

Metformin is a biguanide derivative that has been used for almost seven decades as an Oral Hypoglycaemic agent (OHA) [14]. It is considered as one of the vital drug in treating PCOS women with insulin resistance. It is known to treat anovulation by reducing the concentrations of androgen. Metformin when prescribed in monotherapy, it ameliorated endocrine dysfunction of PCOS [15]. In a combinational therapy along with Clomiphene Citrate (100mg) once daily, Metformin (850mg) twice daily

induced ovulation in women with complaints of obesity and infertility [16]. In this above respective study, the results were compared with monotherapy of Clomiphene Citrate of same dose (100mg) and with combinational therapy of Clomiphene Citrate (100mg) once daily + Pioglitazone (30mg) once daily. Though there were no significance difference in the three different treatments, it was concluded that Metformin can be either prescribed in monotherapy or combinational therapy. Metformin directly acts on theca cells of ovary and reduces the production of androgen. Earlier and sustained effect on hyper-androgenemia was produced by Metformin [17].

In cases of resistance with Clomiphene Citrate, Metformin increased the chances of ovulation rate. This was significance in terms of efficacy when Metformin was included in a three drug regimen (Metformin + Letrozole + Pioglitazone) for Clomiphene Citrate resistant PCOS women [18]. Studies showed that impairment of tyrosine autophophorylation of insulin receptor was responsible for insulin resistance. PCO women with lower levels of autophophorylation of insulin receptor on treating with Metformin showed increased tyrosine activity thereby significantly decreasing insulin resistance [19]. Metformin along with combined oral contraceptives (COC) showed similar efficacy in regulating menstrual cycles and controlling excess androgen receptors such as hirsutism. Adiponectin is a potent mediator of insulin sensitivity and Metformin is known to decrease levels of fasting plasma glucose, homeostasis model assessment (HOMA) index, and fasting serum insulin in PCO women by increasing the levels of adiponectin [20]. Apart from the above uses, pregestational use of Metformin in PCOS women reduced the risk of gestational diabetes mellitus (GDM) [21].

Rosiglitazone is another insulin sensitizing agent that is a selective ligand of nuclear transcription factor peroxisome-proliferator-activated receptor gamma (PPAR$^{\gamma}$) [22]. Generally, all thiazolidinediones exert their action by improving target cell response to insulin without altering pancreatic cell secretion. The activated gamma receptor affects glucose and lipid metabolism. As most of the obese PCOS women show aco-morbidity with insulin resistance, a study revealed that Rosiglitazone treatment showed a decrease in LH/FSH ratio along with significant positive effect on lipid profile and serum insulin. Treatment with Rosiglitazone also showed improvement in endocrine, metabolic and ovulatory response in women with PCOS [23]. When Rosiglitazone and Metformin are compared for their efficacy, Metformin showed better improvement in hyperandrogenemia while Rosiglitazone showed marked effect in insulin resistance and hyperinsulinemia [24]. Pioglitazone action is similar to Rosiglitazone and studies found that Pioglitazone showed a marked improvement in irregular menses, hirsutism and reduction in insulin resistance.

Inositol, a polyalcohol [25] belongs to complex of vitamin B and epimerization of six hydroxyl groups of the Inositol results in the formation of up to nine stereoisomers which further includes both Myo-Inositol (MYO) and D-chiroInositol (DCI). These stereoisomers are indicated as Insulin Sensitizing agents in treating PCOS.

Oral administration of MYO improved clinical features of hyperandrogenism especially hirsutism and acne and regulated metabolic profile of PCOS women. The proposed mechanism of action of MYO and DCI is that it increases the action of insulin, improves ovulatory physiology, and decreases testosterone concentration thereby positively affecting reproductive axis and physiology of hormones [26-28]. Studies note that continued treatment with MYO in PCOS women with obesity resulted in significant weight loss as there was inverse relationship between body mass and treatment efficacy [29]. Deficiency in a specific DIC-containing Inositol phosphoglycan may cause insulin resistance. Inositolphosphoglycans activate enzymes involved in glucose metabolism and administration of DCI reduces insulin resistance and therefore regulates ovarian function and reduces hyperandrogenism. Following a twelve-week treatment with MYO, a positive effect was established for gonadotropin response and pregnancy rate [30].

In PCOS patients with hyperinsulinemia, treatment with N-acetyl cysteine (NAC) improved insulin circulating levels and insulin sensitivity [31]. Bromocriptine is a dopamine antagonist which is therapeutically used to decrease the prolactin levels, increase the secretion of GnRH and induce ovulation. Bromocriptine is the choice of drug for PCOS women with hyperprolactinemia for correcting ovulation. Bromocriptine induces ovulation by reducing the serum prolactin levels [32]. Long term treatment with Bromocriptine in Clomiphene Citrate resistant patients showed a significant reduction in serum prolactin concentration [33].

Liraglutide (GLP-1 agonist) and Roflumilast (PDE-4 inhibitor) role in PCOS:

In a study, a short term monotherapy with Liraglutide and Roflumilast showed a significant weight loss and improved body mass index in obese PCOS women [34]. Liraglutide is a long acting agonist of glucagon-like peptide 1 receptor and acts by stimulating insulin secretion. Roflumilast is a selective antagonist of the enzyme phosphodiesterase [4].

Aromatase Inhibitors:

Letrozole

It is a third generation, selective reversible aromatase inhibitor and it is used for inducing ovulation [35]. Letrozole exerts action by inhibiting the conversion of androgen to estrogeni.e conversion of adrostenedione to estrone. This estrone is one of the naturally occurring estrogen and is seen in elevated levels among PCOS patients. Studies showed treatment with Letrozole in PCOS women resulted in favorable serum levels of progesterone and improved thickness of endometrium thereby increasing the rate of ovulation [36]. Letrozole is considered as an effective second line therapeutic agent in PCOS women who showed little or no response to Clomiphene Citrate as Letrozole increased the endometrial thickness and improved endometrial perfusion. As a first line treatment for inducing ovulation, two doses of Letrozole 5 mg and 7.5 mg per day are considered. A study was conducted to evaluate the significance of two different doses (5 mg and 7.5 mg) of Letrozole and the results showed that there was no significant advantage of using 7.5mg over 5mg of Letrozole in PCOS women [37]. In studies where resistance to Clomiphene Citrate or failure to produce response with Clomiphene Citrate was seen, Letrozole showed to be a suitable ovulation inducing agent in PCOS women [38].

Selective Estrogen Receptor Modulator:

Clomiphene Citrate

It is estrogen receptor modulator that selectively binds to hypothalamic estrogen receptors and blocks the negative feedback mechanism of endogenous estrogen resulting in increased plasma levels of FSH and LH and further favoring the production and release oocytes [18]. Clomiphene Citrate is standard drug for induction or augmentation of ovulation in PCOS women and is referred as gold standard treatment for inducing ovulation [39]. Clomiphene Citrate treatment showed a significant improvement in baseline amenorrhea, total testosterone, anti-mullerian hormone, fasting insulin and improved ovulation rate was observed. Further, treatment with combination of Clomiphene Citrate with Ethinylestardiol for PCOS patients showed a significant increase in pregnancy rate [40]. It was observed in a study that treatment with combination of Clomiphene Citrate and urinary FSH (uFSH) resulted in significantly higher ovulation than uFSH alone. It was also observed in the same study that only less amount of uFSH was required along with Clomiphene Citrate in inducing ovulation [41]. Randomized trials were conducted to compare the effectiveness of Clomiphene Citrate and Tamoxifen and both the drugs were suggested as first line drug for ovulation induction in anovulatory women with PCOS and the results showed that Clomiphene Citrate is more successful than Tamoxifen as a first line therapy for ovulation induction among women with PCOS [42]. A study was conducted to compare Clomiphene Citrate with Letrozole as first line agent in ovulation induction in infertile PCOS women and the results showed that Letrozole was as effective as CC for ovulation induction in infertile PCOS women [43].

Tamoxifen

In patients with normal prolactin levels, Tamoxifen is considered as effective as Clomiphene Citrate in inducing ovulation but with less anti-estrogenic action on endometrium, cervical mucus and granulosa cells [44]. It is a selective Estrogen receptor modulator (ERM) acting by inhibiting aromatase enzyme.

Gonadotropin Treatment:

Gonadotropin therapy (includes FSH and LH) is widely used since late nineties when it was introduced and is considered as second line treatment in inducing ovulation when Clomiphene Citrate treatment fails to achieve pregnancy in PCOS anovulatory women [45]. FSH is released from pituitary and development of ovulatory follicles whereas LH, also released from pituitary is involved with follicle selection, final stages of follicular maturation, follicular rupture and oocyte expulsion with support of corpus luteum formation. The normal levels of FSH in a healthy reproductive women are 4.7-21.5 mIU/ml. An elevated levels of FSH is observed in PCOS.

Subcutaneous administration of recombinant FSH (rFSH) starting with a dose of 37.5IU is adequate to induce follicular growth in PCOS women. GnRH antagonist act by the mechanism of competitive binding to the GnRH receptors in pituitary and suppress gonadotropin release within a few hours [46]. The use of GnRH antagonist in PCOS women was associated with reduction in the incidence of severe ovarian hyper-stimulation syndrome [47]. GnRH antagonist along with low dose of rFSH is considered as cost effective and requires short duration of treatment in infertile PCOS women. Gonadotropins (FSH/hMG (Human menopausal gonadotropin) are also used in combination with Clomiphene Citrate and this decreases the dose required

for optimum ovarian stimulation and also making it as cost effective [39]. In cases of Clomiphene Citrate resistance, Gonadotropins are given in combination with Letrozole which showed acceptable pregnancy rates.

Combined Oral Contraceptives (COC):

Androgenicity can be minimized and menstrual cycles can be regulated with the use of COC [48]. The estrogen increases the sex hormone binding globulin (SHBG) and thus decrease the levels of the free testosterone, whereas the progestin inhibits 5α reductase activity and acts as antagonist for the androgen receptors [49, 50]. Oral contraceptive pills are known to deteriorate insulin sensitivity. Cyproterone acetate and Drospirenone are anti-androgenic progestins present in oral contraceptives and act by blocking peripheral androgen receptors at target organs. Ethinylestardiol (EE) is combined with Drosperinone (progesterogen) where the dose of EE is either 20µg or 30µg and studies found that both doses are having similar effects with a dose of 3mg of Drospirenone [49].

Anti-Androgens

Spironolactone an aldosterone antagonist, diuretic, anti-hypertensive agent is used in PCOS women to ameliorate the effects of hyperandrogenism. It acts primarily at the peripheral region of hair follicle by inhibiting 5α reductase activity. Studies found that PCOS patients when treated with Metformin along with low dose of Spironolactone, resulted in more marked decrease in clinical and biochemical hyperandrogenism than Metformin alone [51].

Flutamide is androgen antagonist that is non-steroidal without any progestogenic or anti-gonadotropic actions [52]. It competitively inhibits androgen receptors. Studies showed that Spironolactone when administered in combination with Cyproterone acetate (CPA)/ Ethinylestardiol (EE) corrects menstrual irregularity. Low dose of Flutamide showed similar efficacy as that of higher dose of Flutamide for treating hirsutism [56]. In women with moderate to severe acne low dose of anti-androgen was found to be effective. The same study showed that low and high doses of CPA with EE were as affective as low dose of Flutamide [57]. A pilot study showed that Finasteride when given at low dose for every three days reduced hirsutism in young patients affected by PCOS or idiopathic hirsutism [58].

Table. 1 Therapeutic options from different type of clinical trials in PCOS patients

S.No.	Year	Author	Type of study	Treatment	Outcome
1	2006	M. Mitkov [24]	Prospective, open, clinical study	Metformin vs Rosiglitazone	Metformin treatment resulted in better response towards hyperandrogenemia whereas Rosiglitazone treatment produced affects more markedly on insulin sensitivity, obesity and hyperinsulinemia.
2	2010	Marzeih Aghahosseini [5]	Open label, clinical trial	Metformin (2500 mg/day)	The outcome with a daily dose of 2500 mg/day of Metformin showed a marked effect on sex hormone-binding globulin (SHBG).
3	2010	Mahmoud S Zakherah [44]	Randomised study	CC + Tamoxifen vs laproscopic ovarian drilling	The study showed that CC along with Tamoxifen is as effective as laproscopic ovarian drilling in both inducing ovulation and pregnancy in PCOS women
4	2011	Ahmed Badawy	Prospective,	Clomiphene Citrate	The outcome of this study showed that

		[42]	randomised trial	vsTamoxifen	Clomiphene Citrate was more successful as first line therapy for ovulation induction in women with PCOS.
5	2012	Su-Ying LIU [54]	Prospective study	Clomiphene Citrate + gonadotropins	The outcome of CC with hMG among PCOS infertile patients who were showing high risk for ovarian hyper stimulation syndrome (OHSS) was found to be safe and efficient.
6	2014	A Mazza [51]	Randomised study	Metformin + Spironolactone	Adding Spironolactone to Metformin resulted in producing a marked reduction of clinical and biochemical hyperandrogenism.
7	2014	Alaa M. Ismail [55]	Randomised clinical trial	l- carnitine	The outcome of adding l-carnitine to Clomiphene Citrate resistant PCOS patients showed an improved quality of ovulation, increased pregnancy rate and improved patient tolerability
8	2015	Ashraf Moini, et al [40]	Randomised control study	Ethinylestardiol and Clomiphene Citrate	The outcome with the combination of EE and CC showed increased clinical pregnancy rates.
9	2016	Sudhindra M Bhattacharya [8]	Randomised study	Drospirenone + 20µg EthinylestardiolvsDrospirenone + 30 µg Ethinylestardiol	Drospirenone + 20 µg of Ethinylestardiol is sufficient to affect the levels of androgen.
10	2016	Waleed El-khayat [18]	Randomised control study	Combination of Letrozole, Metformin and Pioglitazone vs combination of CC, Metformin and Pioglitazone	PCOS women who are resistant to Clomiphene Citrate showed significant pregnancy rates with Letrozole + Metformin + Pioglitazone when compared with patients who took a combination of CC, Metformin and Pioglitazone.

Conclusion

The cumulative result of this search shows that PCOS is a heterogeneous, multifactorial, gynecologic-endocrine disorder which needs immediate attention. The therapeutic options available for PCOS is widely increasing which is a boon for patients who are trying to conceive. The first choice of treatment in PCOS is estrogen receptor modulator which includes Clomiphene Citrate and Tamoxifen. In cases when CC fails or resistance is seen, alternative therapy with gonadotropins and aromatase inhibitors is preferred. Apart from CC, Metformin and MYO are also being considered as first line agents in recent studies. As metabolic syndrome is one of the risk factor for PCOS, insulin resistance should be corrected using insulin sensitizing agents. Excess androgen effects such as hirsutism can be corrected using anti-androgens with the use of Spironolactone, Flutamide and

Cyproterone acetate. Oral contraceptives and combined oral contraceptives are used in the treatment of PCOS to regulate menstrual cycles and correct hyperandrogenism.

Ethical approval:

This article does not contain any studies with human participants or animals performed by any of the authors.

Conflict of Interest

The authors declare that none of them has any conflict of interests

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