



POLYCYSTIC OVARY SYNDROME TREATMENT POSSIBILITIES: FROM CONVENTIONAL THERAPIES TO EMBARKING ON NOVEL STRATEGIES OF CURE

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ABSTRACT

Stein Leventhal Syndrome also commonly known as Polycystic Ovarian Syndrome (PCOS) is a matter of grave concern for a majority of female population of today's generation, who are getting diagnosed with the disorder in whopping numbers. Characterized by menstrual inconsistency (Oligomenorrhea), anovulation (Amenorrhea) and consequent infertility/ subfertility, hormonal imbalances in the body resulting in a host of patho-physiological afflictions in some cases such

as insulin resistance, diabetes, hypothyroidism marked by irritability, difficulty in concentration, sleep apnea, weight gain, hirsutism and even alopecia, PCOS has become the modern mishap especially for the urban populace. As the lifestyle in this age is constantly embarked upon by rising stress levels, as many as upto 25% of women belonging to the reproductive strata are suffering with the syndrome. The present work thus, has tried to enumerate the various therapeutic alternatives- conventional, herbal, ayurvedic, yoga as well as developing methods like neuroendocrine androgen receptors (AR) modulation and brown adipose tissue (BAT) transplant- for treatment and/or management of Stein leventhal syndrome. The motive of the review is to integrate in one place, the different treatment lines

and emerging therapeutic options for Polycystic Ovary Syndrome (PCOS) and associated fertility impediments.

KEYWORDS: PCOS treatment, ovaries, female infertility, alternate therapies, Ayurveda, Yoga, Neuroendocrine Androgen Receptors(AR), Brown Adipose Tissue (BAT).

INTRODUCTION

The aetiology of PCOS or Stein Leventhal Syndrome is the cause of speculation because it is designated with an array of metabolic and hormonal disproportions and at times, is difficult to comprehend.

The Rotterdam criteria, accepted the world over, has laid out the key morphological and diagnostic attributes identified with PCOS as:

1. Scanty periods or absence of menstruation, medically termed as oligomenorrhea or amenorrhea.
2. Androgen excess in serum profile or clinical hyperandrogenism.
3. Polycystic appearance of ovaries in ultrasonographic scan.^[1]

Usually the treatments meant for PCOS target more than one underlying phenomenon and parallel physiological conditions. Generally, oral medications to balance out female reproductive hormones are prescribed along with insulin sensitizing drugs. Since elevated estrogen levels, majorly due to environmental xenoestrogens entering the circulation, are commonly associated with cystic appearance on the ovarian walls and menstrual aberration, usual line of therapy involves either estrogen receptor modulators or Progesterone pills. Sometimes, insulin sensitizing drugs are given alongside for the pervasive insulin resistance. In more severe cases, it becomes imperative to employ other therapies targeting the pituitary and hypothalamus in order to trigger the release of the adequate hormones for menstrual regulation to occur. Surgical methods may be required for persons desiring to conceive. With the ever-increasing figure of PCOS patients, it has become the need of the hour to explore and develop alternate sources and methods of curing the malady. Ayurvedic herbal medicine and Yogic practises such as Kapalabhati, seem to be up-and-coming as exceedingly promising solutions or at least managereal options for infertility as suggested by studies and acceptance under popular culture nowadays. A couple of revolutionizing findings targeting Neuroendocrine Androgen Receptors (AR) and Brown Adipose Tissue (BAT) transplant hint towards novel therapeutic as well as preventive possibilities in the near future.

Conventional Allopathic Treatments for Polycystic Ovarian Syndrome and Clinical Infertility in Females

1. Clomiphenes

Clomiphene citrate is an antiestrogen, an estrogen receptor modulator, particularly acting on the Hypothalamus, Pituitary and Ovaries, causing release of Follicle Stimulating Hormone (FSH) and Leutenizing Hormone (LH) to induce ovulation. Administered orally, with an optimum dosage of 50mg/day,^[2] has been effectively used to treat subfertility and anovulation in case of PCOS, has substantial evidence – over 70 percent success rates - establishing the occurrence of conception^[3] and has often been considered as the *'first line of treatment'* by practitioners when countering fertility issues.^[4] The practise of applying combination medicine to the patients of oligo or anovulation has been notably efficacious. Clomiphene citrate has been administered orally, in combination with coenzyme Q10(coQ10) to those females complaining of clomiphene citrate resistant PCOS, and has proved to be extremely constructive a dose.^[5] A combination therapy of clomiphene citrate along with Human Menopausal Gonadotrophin (HMG), Corticosteroids and/or Follicle Stimulating Hormone (FSH) is employed to stimulate Ovulation and assisted reproductive treatments.^[6]

2. Letrozole

A primary consideration for PCOS treatment, letrozole – an aromatase inhibitor - is on par with clomiphene, based on clinical trials and thus one of the most prescribed drugs for the therapy.^[7] The optimum dosage has been stipulated to be between 5 and 7.5 mg/day^[8,9] via the oral route of administration. Other studies implied letrozole to be a better alternative to clomiphene with ample statistical data to support the evidence of live birth as opposed to its counterpart, higher rate of ovulation but, with certain complications as congenital deformities as well as giddiness amongst some patients.^[10] The reduced chances of multiple pregnancies when recruited alongside reproductive assistant technology such as Artificial Insemination too place it on the most prospective treatment option.^[11]

3. Metformin

The women suffering from Stein Leventhal syndrome often stand the risk of of developing Type 2 Diabetes Mellitus and obesity as a result of poor metabolism and insulin resistance along with an array of other conditions such as dislipidemia, cardiovascular disorders, hyperstension etc.^[12] The role of Metformin , an antihyperglycemic drug taken orally, as a direct treatment option to alleviate the cysts appearing over the ovarian wall per se had been a

subject of research and speculation.^[13] Yet the dosage could be anywhere between 1000 mg/day to 1700mg/day and has proven to be effective enough to regulate the circulatory insulin levels, in turn helping establish metabolic stability and restoring periodic normalcy.^[14] But over the course of time, metformin has increasingly been observed to be of immense significance for ovulation induction and restoring the normalcy of the menstrual cycle by curbing diabetes like symptoms and enhance the sensitivity of the glucose receptors for glycemic uptake^[15] and thus its use has been characterized as effective therapeutic alternative for Polycystic ovarian syndrome(PCOS).

4. Tamoxifens

A highly competent oral substitute drug to letrozole, Tamoxifen citrate, a Selective Estrogen Receptor Modulator(SERM), remains a reliable choice of treatment for PCOS more so, in clomiphene citrate resistant patients, with an optimum dose of 20 mg/day^[16] generating ovulation amongst as many as above 75% of the suffering women based on studies.^[17] But, compared to the first – line therapy that is Clomiphene for the disorder, tamoxifens appear to be less efficacious.^[18] Yet it is preferred in case of intolerance to clomiphene citrate treatment because tamoxifen citrate can still produce results similar to clomiphene and is a potential drug for managing menstrual irregularities.^[19,20]

5. Progestins - Drospirenone

Since the diagnosis of PCOS is usually indicative of excessive estrogen or low levels serum progesterone, often accompanied by hyperandrogenism, a promising candidate for alleviation of ovarian cysts and the treatment of amenorrhea, could be Drospirenone (DRSP) – a progesterone derivative in the form of a Combined Oral Contraceptive(COC).^[21] A dosage of 3 mg/day of DRSP has also been indicative of great responses, apart from combined form which could range anywhere between 0.5 to 2 µg when combined with Ethinylestradiol(EE).^[21] It targets not only serum testosterone levels, has shown to lower the plasma concentrations of Leutenizing Hormone(LH), Sex Hormone Binding Globulin (SHBG) over successive cycles and thus the effects of hyperandrogenism have been subsided with consistent usage over 12 menstrual cycles in the complainants of PCOS^[22] with other symptoms such as hirsutism being significantly relieved^[23] yet the indication that its use may pave way for hemostasis or venous thromboembolism^[24] has well been documented and is quite gruesome.

6. Gonadotropins

Falling under the category of second-line-treatment for anovulatory infertility, as well as in cases where one is resistant to clomiphene treatment, Gonadotropins have long been impressively potent, yet safe in enhancing the birth rate following ovulation induction in subfertile and/or amenorrheic females owing to PCOS^[25] as well as low levels of gonadotrophins. Dosed timely during sexual intercourse or as intrauterine injection(IUI) or intramuscular injection(IM), low levels of Gonadotropins (recombinant Follicle Stimulating Hormone or rFSH and human menopausal gonadotropin or HMG) is delivered exogenously.^[4] Since Gonadotropins as a treatment option pose the risk of Hyper Ovulatory Stimulation and thus multiple pregnancies, therefore, periodic low dose of FSH or HMG intake is advised i.e. between 50 IU/day to 75IU/day, along with progestins in some cases.^[26,27] As such, exogenous administration of FSH has shown reliable results for follicular development and ovulation when compared to Combined Oral Contraceptives (COC)^[28], as well as increased high instances of live birth rates and pregnancy when combined with metformin,^[29] yet cost of administration is surely a cause of concern.

7. Gonadotropin release Hormone agonists(GnRHa)

Ovulation can be stimulated using one time shot of a GnRH agonist right before *in-vitro* fertilization(IVF), which causes LH and FSH surge and subsequent ovulation, at the same time reducing ovarian hyperstimulation.^[30] The overall pregnancy rates when in combination with clomiphene, have been quite significant amongst the recipients over time.^[30] Ovulation rates in case of GnRHa have been much higher when compared to GnRH antagonists as observed during therapeutic trials although pregnancy rates are comparable for the two.^[31] A pulsatile administration of GnRHa alone or in combination with gonadotropins is routinely used in PCOS as well as hypothalamic amenorrhea.^[32] Again the expenses of the treatment are higher.

8. Laparoscopy

The surgical drilling of ovaries or Laparoscopic Ovarian Drilling (LOD) to rid of cysts is not new but the method is generally reserved for cases where the initial treatments failed to do any good. It is a safe alternative to manage subfertility and is employed for patients who respond to the first line of treatment poorly, but can have adverse iatrogenic effects and is not a definitive treatment.^[33] Surgery is generally performed right before gonadotropin administration in order to reduce ovarian hyperstimulation, and the resultant multiple

pregnancies in patients seeking Assisted Reproductive Technology(ART).^[34] Laser techniques and monopolar electrocautery also act by reducing androgen levels and aromatization of steroids to estrone thus reducing circulatory estrogen and androgen levels alike and subsiding the symptoms of PCOS, though it is expensive as an option.^[4]

Table 1: Tabular representation of conventional treatment options, their action, mode of administration and effects.

Drug or technique	Target	Route of Administration	Effect
Clomiphene Citrate	Estrogen receptors (ERs) in hypothalamus	Oral (100mg/day or as prescribed)	Anti-estrogenic effects, lowers serum estrogen levels, increases follicular phase FSH and LH levels
Letrozole	Aromatase, Hypothalamus-pituitary- ovarian axis	Oral(5mg/day or as prescribed)	Ovulation, increases Gonadotropin Release Hormone (GnRH), FSH and decreases estrogen
Metformin	Glucose Transporter 4 (GLUT4)	Oral (upto 1700mg/day or as prescribed)	Peripheral Glucose uptake and regulation
Tamoxifen Citrate	Estrogen Receptors(ERs)	Oral (20mg/day or as prescribed)	Anti-estrogenic effects, lowers serum estrogen levels
Drospirenone	Progesterone Receptors(PRs)	Oral (3mg/day or as prescribed)	Increases Progesterone, FSH, reduces testosterone, ovulation
Gonadotropins	Follicle Stimulating Hormone Receptors (FSHRs) in ovaries, uterus	Injection –Intrauterine (IUI) or Intramuscular (IM) (50-75 IU/day)	Follicular development, ovulation, also used for conception in Assisted Reproductive Technology (ART)
Gonadotropin Release Hormone agonists (GnRH _a)	Pituitary gonadotrophs receptors	Pulsatile infusion using computerized pump (5-20mcg/90 minutes), Intravenous injection (IVI)	Ovulation, used in ART
Laparoscopy	Ovaries	Surgical procedure requiring ovarian drilling	Removal of fluid filled cysts from ovarian walls

Alternate Therapies/Treatments for Polycystic Ovarian Syndrome and Clinical Infertility in Females

1. Curcumin

A phenolic curcuminoid found in the plant *Curcuma longa*, commonly known as *Haldi* in Indian households, has been studied to have extremely positive impacts when it came to

restoring the normal hormonal profile, restoring periodicity as well as dissolution of ovarian cysts in PCOS in rat models,^[35] other than reduction in insulin levels in case of insulin resistant PCOS,^[36,37] even as its anti-inflammatory and anti-oxidant effects have been long known to world with zero adverse affects. Thus, Curcumin could well be included in the mainstream for a potential candidate for PCOS treatment as it continues to be a regular one in home remedies for various ailments, menstrual disorders included.

2. *Asparagus racemosus*

Known as *Shatavari* in ayurvedic terms, *Asparagus racemosus* is a phytoestrogen and has a number of pharmacological activities including anti-inflammatory properties, immunomodulatory effects, antimicrobial properties, also lactational effects^[38,39] and has shown striking results in restoring menstrual regularity, promoting follicular maturation and preparing the womb for conception according to some studies^[38,40] with little to no side effects.

3. *Commiphora mukul* or *Commiphora wightii*

A widely used component in the medications for PCOS therapy in Ayurvedic system of medicine, *Commiphora mukul*, also known as Guggulu (the plant exudate)- an ole gum resin having photymedicinal attributes- has been widely studied now for its curative properties^[41,42] for treating metabolic disorders like hypothyroidism^[43] as well as menstrual disorders in rat models for substantiating evidence of cure and is as such, routinely prescribed in alternate system of medicine for patients suffering from these diseases. The plant extracts from *Commiphora wightii* have been recently researched and the therapeutic effects been concluded in extenuating PCOS symptoms as well as hyperandrogenism in case of DHEA (Dehydroepiandrosterone) induced polycystic ovaries when tested with rat models.^[44]

4. Lifestyle modifications combined with Herbal Medicine

Data of preclinical and clinical trials comprising of 762 women being subjected to herbal extracts of *Vitex agnus-castus*, *Cimicifuga racemosa*, *Tribulus terrestris*, *Glycyrrhiza spp.*, *Paeonia lactiflora* and *Cinnamomum cassia* is remarkably suggestive of alleviating oligomenorrhoea or anovulatory infertility associated with PCOS, enhancing the findings when combined with lifestyle modifications such as mild to moderate exercise.^[45,46] As yet, herbal systems of medications do require further organized studies for them to be fully accepted even though they have no adverse effects upon the user.

5. Yoga and Pranayam

Yoga (yogic physical exercises) and pranayama (or yogic breathing techniques) have been accepted and are now being practiced and propagated the world over for their beneficial effects on health. Whereas exercise has been known to help maintain weight and thus manage PCOS more so, in lean patients than obese PCOS complainants.^[47] But several studies have been conducted in India (the land of Yoga), as well as across the globe which corroborate the significance of Yoga in managing symptoms of PCOS and ovarian dysfunction along with associated metabolic disruptions, anxiety, depression.^[48] A particular yogic breathing technique called Kapalbhathi has been scrutinized and discerned for its potential in helping with clinical infertility in PCOS patients.^[49] A systematic study has established the pre-eminence of holistic Yoga program over general exercise plan in balancing out the hormones, maintaining the weight and thus easing of the menstrual dysfunction owing to PCOS in pubertal females.^[50]

Evolving Avenues for Infertility Treatment and PCOS

1. Targeting Neuroendocrine Androgenic Receptor

It has been concluded that Neuronal endocrine Androgen Receptors(AR) play a key role in development of PCOS and associated infertility and that blocking or modulating these neuroendocrine AR on a genomic level can very well prevent the onset of PCOS and related features in mouse models.^[51] Thus, targeting or modulating the AR in neurons (rather than in ovarian granulosa cells) can be a groundbreaking therapeutic recourse for anovulatory infertility and hyperandrogenism in the near future as suggested by the latest findings.

2. Brown Adipose Tissue(BAT) Transplantation

In mouse models with Dehydroepiandrosterone (DHEA) instigated PCOS, it was found that implantating Brown Adipose Tissue(BAT) very well mitigated the features of oligomenorrhea linked to infertility and alleviated PCOS.^[52] There have been other studies which prove people having metabolically active BAT tend to live longer, have healthy metabolism and age later in life. Hence, such studies are suggestive of a novel treatment such as BAT transplantation in case of PCOS.

DISCUSSION

Even though the prevalence of the rogue called Polycystic Ovarian Syndrome (PCOS) is not something new but its ever-increasing instances among the reproductive women of all age groups has called for better understanding of its treatment options. The present review has

tried to put the most sought after as well as the lesser known alternate therapies for menstrual irregularities in PCOS, in a frame. Whereas the conventional methods have been quite effective in treating the disorder, yet have their own side effects too. A host of other related complications requires a more target specific as well as safer options for treating the same. As much as herbal medicine, ayurveda, yoga are gaining popularity among the masses, recent studies have proven them to be curative for PCOS as well as other metabolic disorders to a great extent. A more thorough research may well substantiate these findings. The findings pertaining to neuronal AR and BAT transplant too open up newer directions to more specific methods in combating PCOS and prevent its occurrence in the future to come & hold great prospects for innovative new therapies in the field of infertility treatment.

REFERENCES

1. M. E. Lujan, D. R. Chizen, and R. A. Pierson, "Diagnostic Criteria for Polycystic Ovary Syndrome: Pitfalls and Controversies," *J. Obstet. Gynaecol. Canada*, 2008; 30(8): 671–679.
2. P. Dasari and G. Pranahita, "The efficacy of metformin and clomiphene citrate combination compared with clomiphene citrate alone for ovulation induction in infertile patients with PCOS.," *J. Hum. Reprod. Sci.*, 2009; 2(1): 18–22.
3. R. Davidson, T. Motan, and C. Korownyk, "Clomiphene for anovulatory infertility," *Can. Fam. Physician*, 2016; 62(6): 492.
4. Melo AS, "Treatment of infertility in women with polycystic ovary syndrome.," *Ann. Endocrinol. (Paris)*., 2010; 71(3): 225–227.
5. A. El Refaey, A. Selem, and A. Badawy, "Combined coenzyme Q10 and clomiphene citrate for ovulation induction in clomiphene-citrate-resistant polycystic ovary syndrome," *Reprod. Biomed. Online*, 2014; 29(1) 119–124.
6. H. Sovino, T. Sir-Petermann, and L. Devoto, "Clomiphene citrate and ovulation induction," *Reprod Biomed Online*, 2002; 4(3): 303–310.
7. A. Ghahiri, N. Mogharehabed, and M. Mamourian, "Letrozole as the first-line treatment of infertile women with poly cystic ovarian syndrome (PCOS) compared with clomiphene citrate: A clinical trial.," *Adv. Biomed. Res.*, 2016; 5(6).
8. F. R. Zadeh, M. M. Aghsa, and R. Nasiri, "109 a Randomized Trial of Ovulation Induction With Two Different Doses of Letrozole in Women With Pcos," *Reprod. Biomed. Online*, 2010; 20P: S45.
9. E. Rahmani, S. Ahmadi, N. Motamed, and H. Maneshi, "Dosage Optimization for

- Letrozole Treatment in Clomiphene-Resistant Patients with Polycystic Ovary Syndrome: A Prospective Interventional Study,” *Obstet. Gynecol. Int.*, 2012: 1–4.
10. R. S. Legro *et al.*, “Letrozole versus Clomiphene for Infertility in the Polycystic Ovary Syndrome,” *N. Engl. J. Med.*, 2014; 371(2): 119–129.
 11. S. Kar, “Current evidence supporting ‘letrozole’ for ovulation induction,” *J. Hum. Reprod. Sci.*, 2013; 6(2): 93–8.
 12. R. Bentley-Lewis, E. Seely, and A. Dunaif, “Ovarian hypertension: Polycystic ovary syndrome,” *Endocrinol. Metab. Clin. North Am.*, 2011; 40(2): 433–449.
 13. H. Lashen, “Review: Role of metformin in the management of polycystic ovary syndrome,” *Ther. Adv. Endocrinol. Metab.*, 2010; 1(3): 117–128.
 14. A. M. Fulghesu *et al.*, “Is there a dose-response relationship of metformin treatment in patients with polycystic ovary syndrome? Results from a multicentric study,” *Hum. Reprod.*, 2012; 27(10): 3057–3066.
 15. N. P. Johnson, “Metformin use in women with polycystic ovary syndrome,” *Ann. Transl. Med.*, 2014; 2(6): 56.
 16. E.-G. M.N., M. A.E., and F. M.A., “Comparison of letrozole versus tamoxifen effects in clomiphene citrate resistant women with polycystic ovarian syndrome,” *J. Reprod. Infertil.*, 2015; 16(10): 30–35.
 17. V. Suri, S. Sahdev, L. Dhaliwal, and K. Gupta, “Tamoxifen: An alternative to clomiphene in women with polycystic ovary syndrome,” *J. Hum. Reprod. Sci.*, 2011; 4(2): 76.
 18. A. Badawy and A. Gibreal, “Clomiphene citrate versus tamoxifen for ovulation induction in women with PCOS: A prospective randomized trial,” *Eur. J. Obstet. Gynecol. Reprod. Biol.*, 2011; 159(1): 151–154.
 19. R. Boostanfar, J. K. Jain, D. R. Mishell Jr., and R. J. Paulson, “A prospective randomized trial comparing clomiphene citrate with tamoxifen citrate for ovulation induction,” *Fertil Steril*, 2001; 75(5): 1024–1026.
 20. V. C. Y. Lee and W. Ledger, “Aromatase inhibitors for ovulation induction and ovarian stimulation,” *Clin. Endocrinol. (Oxf)*, 2011; 74(5): 537–546.
 21. R. Mathur, O. Levin, and R. Azziz, “Use of ethinylestradiol/drospirenone combination in patients with the polycystic ovary syndrome,” *Ther. Clin. Risk Manag.*, 2008; 4(2): 487–492.
 22. M. Guido *et al.*, “Drospirenone for the treatment of hirsute women with polycystic ovary syndrome: A clinical, endocrinological, metabolic pilot study,” *J. Clin. Endocrinol. Metab.*, 2004; 89(6): 2817–2823.

23. C. Batukan and I. I. Muderris, "Efficacy of a new oral contraceptive containing drospirenone and ethinyl estradiol in the long-term treatment of hirsutism," *Fertil. Steril.*, 2006; 85(2): 436–440.
24. C. Q. Wu, S. M. Grandi, K. B. Filion, H. A. Abenhaim, L. Joseph, and M. J. Eisenberg, "Drospirenone-containing oral contraceptive pills and the risk of venous and arterial thrombosis: A systematic review," *BJOG An Int. J. Obstet. Gynaecol.*, 2013; 120(7): 801–810.
25. D. Hamilton-Fairley, D. Kiddy, H. Watson, M. Sagle, and S. Franks, "Low-dose gonadotrophin therapy for induction of ovulation in 100 women with polycystic ovary syndrome.," *Hum. Reprod.*, 1991; 6(8): 1095–9.
26. T. Practice and R. Medicine, "Use of exogenous gonadotropins in anovulatory women: a technical bulletin," *Fertil. Steril.*, 2008; 90(5): 7–12.
27. A. Gorry, D. M. White, and S. Franks, "Infertility in polycystic ovary syndrome: focus on low-dose gonadotropin treatment.," *Endocrine*, 2006; 30(1): 27–33.
28. A. M. Van Heusden, H. J. T. Coelingh Bennink, and B. C. J. M. Fauser, "FSH and ovarian response: Spontaneous recovery of pituitary-ovarian activity during the pill-free period vs. exogenous recombinant FSH during high-dose combined oral contraceptives," *Clin. Endocrinol. (Oxf)*, 2002; 56(4): 509–517.
29. S. Palomba, A. Falbo, and B. La Giovanni, "Metformin and gonadotropins for ovulation induction in patients with polycystic ovary syndrome: a systematic review with meta-analysis of randomized controlled trials.," *Reprod. Biol. Endocrinol.*, 2014; 12(3).
30. A. H. Farag, M. H. N. El-Deen, and R. M. Hassan, "Triggering ovulation with gonadotropin-releasing hormone agonist versus human chorionic gonadotropin in polycystic ovarian syndrome. A randomized trial," *Middle East Fertil. Soc. J.*, 2015; 20(4): 217–223.
31. M. S. Trenki??, J. Popovi??, V. Kopitovi??, A. Bjelica, R. ?? ivadinovi??, and S. Pop-Trajkovi??, "Flexible GnRH antagonist protocol vs. long GnRH agonist protocol in patients with polycystic ovary syndrome treated for IVF: Comparison of clinical outcome and embryo quality," *Ginekol. Pol.*, 2016; 87(4): 265–270.
32. N. Magon, "Gonadotropin releasing hormone agonists: Expanding vistas," *Indian J. Endocrinol. Metab.*, 2011; 15(4): 261.
33. P. Nayak, S. Agrawal, and S. Mitra, "Laparoscopic ovarian drilling: An alternative but not the ultimate in the management of polycystic ovary syndrome," *J. Nat. Sci. Biol. Med.*, 2015; 6(1): 40.

34. I. Lebbi, R. Ben Temime, A. Fadhlaoui, and A. Feki, "Ovarian Drilling in PCOS: Is it Really Useful?," *Front. Surg.*, 2015; 2(6): 1–3.
35. P. S. Reddy, N. Begum, S. Mutha, and V. Bakshi, "Beneficial effect of Curcumin in Letrozole induced polycystic ovary syndrome," *Asian Pacific J. Reprod.*, 2016; 5(2): 116–122.
36. S. Mohammadi, L. K. Bardei, V. Hojati, A. Ghorbani, and M. Nabiuni, "Anti-Inflammatory Effects of Curcumin on Insulin Resistance Index, Levels of Interleukin-6, C-Reactive Protein, and Liver Histology in Polycystic Ovary Syndrome-Induced Rats Citation: Mohammadi Sh, Karimzadeh Bardei L, Hojati V, Ghorbani A, Nabiuni M. Ant," *CELL JOURNAL(Yakhteh)*, 2017; 19(3): 425–433.
37. B. B. Aggarwal and T. 77030 Cytokine Research Laboratory, Department of Experimental Therapeutics, The University of Texas M.D. Anderson Cancer Center, Houston, "Targeting Inflammation-Induced Obesity and Metabolic Diseases by Curcumin and Other Nutraceuticals," *Cancer*, 2011; 173–199.
38. S. Alok, S. K. Jain, A. Verma, M. Kumar, A. Mahor, and M. Sabharwal, "Plant profile, phytochemistry and pharmacology of *Asparagus racemosus* (Shatavari): A review," *Asian Pacific J. Trop. Dis.*, 2013; 3(3): 242–251.
39. O. Article, "A Double-Blind Randomized Clinical Trial for Evaluation of Galactogogue Activity of *Asparagus racemosus* Willd, 2009; 10(6): 167–172.
40. B. Talal and A. Hamad, "Asparagus racemosus – Monograph," 2016.
41. P. Sarup, S. Bala, and S. Kamboj, "Pharmacology and Phytochemistry of Oleo-Gum Resin of *Commiphora wightii* (Guggulu)," *Scientifica (Cairo)*., 2015; 1–14.
42. R. B. Singh, M. A. Niaz, and S. Ghosh, "Hypolipidemic and antioxidant effects of commiphora mukul as an adjunct to dietary therapy in patients with hypercholesterolemia," *Cardiovasc. Drugs Ther.*, 1994; 8(4): 659–664.
43. S. Panda and A. Kar, "Guggulu (*Commiphora mukul*) potentially ameliorates hypothyroidism in female mice," *Phyther. Res.*, 2005; 19(1): 78–80.
44. A. Kavitha, N. B. A, S. K. M, and V. K. S, "Evaluation of effects of *Commiphora Wightii* in Dehydroepiandrosterone (Dhea) induced Polystic Ovary Syndrome (Pcos) In Rats," 2016; 4(1).
45. S. Arentz, J. A. Abbott, C. A. Smith, and A. Bensoussan, "Herbal medicine for the management of polycystic ovary syndrome (PCOS) and associated oligo / amenorrhoea and hyperandrogenism ; a review of the laboratory evidence for effects with corroborative clinical findings," 2014.

46. S. Arentz, C. A. Smith, J. Abbott, P. Fahey, B. S. Cheema, and A. Bensoussan, "Combined Lifestyle and Herbal Medicine in Overweight Women with Polycystic Ovary Syndrome (PCOS): A Randomized Controlled Trial," no. May, 2017.
47. A. Khademi, A. Alleyassin, M. Aghahosseini, L. Tabatabaeefar, and M. Amini, "The effect of exercise in PCOS women who exercise regularly," *Asian J. Sports Med.*, 2010; 1(1): 35–40.
48. S. E. Agapova, T. Cameo, A. B. Sopher, and E. Sharon, "HHS Public Access," 2015; 32(3): 194–201.
49. R. Ansari, "Kapalabhati pranayama: An answer to modern day polycystic ovarian syndrome and coexisting metabolic syndrome?," *Int. J. Yoga*, 2016; 9(2): 163.
50. R. Nidhi, V. Padmalatha, R. Nagarathna, and R. Amritanshu, "Effects of a Holistic Yoga Program on Endocrine Parameters in Adolescents with Polycystic Ovarian Syndrome: A Randomized Controlled Trial," *J. Altern. Complement. Med.*, 2013; 19(2): 153–160.
51. A. S. L. Caldwell *et al.*, "Neuroendocrine androgen action is a key extraovarian mediator in the development of polycystic ovary syndrome," *Proc. Natl. Acad. Sci.*, 2017; 114(16): E3334–E3343.
52. X. Yuan *et al.*, "Brown adipose tissue transplantation ameliorates polycystic ovary syndrome," *Proc. Natl. Acad. Sci.*, 2016; 113(10): 2708–2713.