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HERBAL REMEDIES FOR STEIN-LEVENTHAL SYNDROME, A FAST SPREADING INFERTILITY DISORDER: A REVIEW

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ABSTRACT

Stein-Leventhal syndrome or Polycystic Ovarian Syndrome (PCOS) is a heterogeneous endocrine disorder that affects about one in 15 women worldwide. It is a major disorder characterized by elevated levels of male hormones (androgens), acne and hirsutism. It can even cause insulin resistance, anovulation and infertility on prolonged incidence of cysts. Infertility in female is very often observed. It is inability to conceive and produce the child. ART (Assisted Reproductive Technology) has been carried out such as IVF, ICSI but common people cannot afford the cost of such procedures. Various allopathic, Ayurvedic and other alternative medicines and physiotherapy with acupuncture are been effective to enhance the pregnancy and these drugs and exercises will even prevent the recurrent abortions. In this regard the present review is aimed to provide all the necessary information regarding the effective method for treatment of female infertility. Since PCOS is a curable disorder, it can be cured by use of natural remedies. The natural remedies include treatment with phytoestrogenic and non-estrogenic herbs such as Ashoka, Liquorice, Ginseng, Black cohosh, Dong quai, Hops and Kelp which are effective and safe. In this review, an attempt has been made to study the use of aural remedy for treatment of PCOS.

Key words: Stein-Leventhal syndrome, natural remedies, Ashoka, Cinnamon, Liquorices, and Ginseng.

INTRODUCTION

Stein-Leventhal syndrome or polycystic ovarian syndrome (PCOS) is the most common disorder in women of reproductive age as well as premenopausal women [1]. This is a type endocrine disorder which involves an ovulation, hirsutism, irregular and painful menstrual cycles, amenorrhea, having small cysts in the ovaries etc. This is a major cause of infertility in women, also known as stein-levities syndrome [2]. Clinically, PCOS is made up of three characteristics: hyperandrogenic state, an ovulation and insulin resistance [3,4] the accompanying insulin resistance and hyperinsulinemia mark PCOS as a prediabetic state, with high incidence of impaired glucose tolerance, gestational diabetes, and overt diabetes. In patients with PCOS, other

metabolic and biochemical changes, such as hypertension and dyslipidemia, increase the risk of cardiovascular disease. Herbs can be defined generally in commerce as a plant, plant part or extract thereof used for flavour, fragrance or medicinal purposes. Traditional herbal medicines are naturally occurring substances with minimal or no industrial processing that have been used to treat various illnesses. Traditional herbal medicines are getting significant attention in global health debates. Traditional medicine has established promotive, preventive, curative and rehabilitative role [5]. According to Ayurveda PCOS is caused by the imbalance of the three *doshas* in which aggravated *kapha* affects the functions of *vata* and *pitta* by which *ras* and *rakta* dhatu

get affected with formation of *Ama* (toxins) in weaker channels of the body affecting *artav-vaha strotus* which is responsible for reproduction in female body. Benefit of herbal therapy compared to conventional therapy is that herbal therapy is safe with lesser side effects and presence of multiple active compounds in medicinal herbs altogether provides a potentiating effect [6,7].

Causes of PCOS

Following are few important causes of PCOS:

- 1) Genetic predisposition
- 2) Strong stimulation in adrenals in childhood
- 3) Raised insulin levels
- 4) Contraceptive pills & Fast food consumption
- 5) Hormonal imbalance
- 6) Stress & Lack of physical exercise

Sign and Symptoms of PCOS

The principal signs and symptoms of PCOS are: Irregular or absence of periods, Acne, Excess body hair (hirsutism), Weight gain or difficulty losing weight, Pain in Pelvic region, Elevated Luteinizing Hormone (LH) and decreased, Follicle stimulating hormone (FSH), Infertility (difficulty becoming pregnant) [8].

Histological Features of PCOS

Histological features of PCOS includes: Whole ovarian hypertrophy, Thickened capsule ($>100\ \mu$), Increased number of sub capsular follicle cysts. Scarcity of corporea lutea or albicantia, Hyperplasia and fibrosis of the ovarian stroma, Premature luteinization of theca cells [9].

Allopathic Therapy for PCOS

Various Treatment of Female Infertility or Fertility promoting agent. Fertility drugs are often used alone as initial treatment to induce ovulation. If they fail as sole therapy, they may be used with assisted reproductive procedures, such as in vitro fertilization, to produce multiple eggs, a process called *superovulation*. According to the American Society for Reproductive Medicine, fertility drugs can be divided into three main categories:

- ✓ Medications for Ovarian Stimulation. Clomiphene (Clomid, Serophene); letrozole (Femara), follicle stimulating hormone (FSH) (Follistim, Gonal-F, Bravelle) human menopausal
- ✓ Gonadotrophin (hMG) (Humegon, Repronex, Menopur); luteinizing hormone (LH) (Luvris)
- Medications for Oocyte Maturation, Human chorionic gonadotropin (hCG) [Profasi, APL, Pregnyl, Novarel, Ovidrel]
- ✓ Medications to Prevent Premature Ovulation. GnRh agonists (Lupron and Synarel); Gn RH antagonists (Antagon, Cetrotide [9,10])

- ✓ Some other agent like Nafarelin-a specific gonadotropin-releasing hormone agonist, Trilazone, Clomiphene, Metformin, Spironolactone, Laparoscopy [11-16].

Ovarian Failure Treatment for Female Infertility

Ovarian Failure Between 20 - 30 % of female infertility can be blamed on ovulatory problems. Ovulation is regulated by hormone activity. Thus, several hormonal problems can prevent ovulation, fertilization or implantation of the egg. Below is a description of the most common hormone irregularities in women which cause reproductive difficulty. Mechanical obstructions account for up to 25 - 40 % of female infertility problems. Adhesions, scar tissue and blockages that affect the fallopian tubes and uterine cavity can prevent fertilization and implantation (Table 1 & 2).

MEDICINAL HERBS IN PCOS

Ginseng saponin

Botanical Name: *Panax ginseng*, Family: Araliaceae, Female Sprague-Dawley rats (190-210 g) were induced polycystic ovary with intramuscular injection of Estradiol Valerate (EV) and separated into three groups: EV control (n=10), EV plus Ginseng Total Saponins (n=10), and oil control (n=10). Ovarian morphology and Nerve Growth Factor (NGF) protein expression were observed. Increased expression of Nerve Growth Factor was noted in the ovaries and the brain of rats with Poly Cystic Ovary. Ginseng Total Saponins administration attenuated NGF expression in the ovaries [22].

Linseed cynogenetic glycoside

Botanical Name: *Linum usitatissimum*, Family: Linaceae In this study the impact of flaxseed supplementation (30g/day) on hormonal levels in a 31-year old woman with PCOS was observed. During a four month period, the patient consumed 83% of the flaxseed dose. Height, weight measurement and fasting blood samples taken at baseline and 4-month follow-up indicated significant decrease in Body Mass Index (BMI), insulin, total serum testosterone and free serum testosterone levels. The patient also reported a decrease in hirsutism at the completion of the study period. The clinically-significant decrease in androgen levels with a concomitant reduction in hirsutism reported in this case study [23].

Mentha oil preparation

(Botanical Name: *Mentha spicata*, Family: Labiatae). The study was carried out in Turkey in a two centre as 30 day randomized controlled trial. Forty two volunteers were randomized to take spearmint tea twice a day for a 1 month period and compared with a placebo herbal tea. At 0, 15 and 30 days of the study serum

androgen hormone levels and gonadotropin were checked; the degree of hirsutism was clinically rated. 41 out of 42 patients completed the study. Free and total testosterone levels and degree of hirsutism were reduced over the 30 day period in the spearmint tea group. LH and FSH were increased. It was demonstrated and confirmed that spearmint has antiandrogen properties [24].

Cinnamon

(Botanical Name: *Cinnamomum zeylanicum*, Family: Lauraceae) Cinnamon extract has been shown to reduce insulin resistance in in vitro and in vivo studies by increasing phosphatidyl inositol 3-kinase activity in the insulin signaling pathway and thus potentiating insulin action. Fifteen women with polycystic ovary syndrome (PCOS) were randomized to daily oral cinnamon and placebo for 8 weeks. Comparisons of post-treatment to baseline insulin sensitivity indices using fasting and 2-hour oral glucose tolerance tests showed significant reductions in insulin resistance in the cinnamon group but not in the placebo group [25].

Milk thistle Flavonoid

(Botanical Name: *Silybum marianum*, Family: Asteraceae) In this study, the effect of silymarin which is known to have insulin sensitivity effects on the levels of glucose, insulin, testosterone, leutinizing hormone (LH) and progesterone was tested. Ovulation rate and Homeostasis Model Assessment of insulin Resistance (HOMA) ratio were determined. 3-months of treatment were conducted in 60 PCOS patients in three well-matched groups. The first one (n=20), received silymarin (750mg/day). The second group received metformin (1500mg/day) while the third group treated by combination of metformin (1500mg/day) and silymarin (750mg/day). All these groups had taken the drugs in divided doses. The results showed significant increment in progesterone levels after completion of treatment. In conclusion the addition of silymarin to metformin in treatment of PCOS patients has improving effect on disturbed hormones and ovulation rate [26].

Kasip Fatimah

(Botanical Name: *Labisia pumila* var. *alata*, Family: Myrsinaceae) In this study, effect of a Malaysian herb Kasip Fatimah had been checked on 9 week old PCOS rats. PCOS was induced in female rats before puberty by treating continuously with dihydro testosterone. The PCOS rats were randomly subdivided into two groups; PCOS herb treated and PCOS control. PCOS herb treated rats received a daily oral dose of (50mg/kg body weight), dissolved in 1 ml of de ionized water, for 4-5 weeks. PCOS controls received 1 ml of deionised water on the same schedule. Result showed reducing body weight gain in ovariectomized rats. Herb treatment increases uterine weight, indicating estrogenic

effects and improves insulin sensitivity and lipid profile in PCOS rats without affecting body composition [27].

Astragalus polysaccharide

(Botanical Name: *Astragalus* spp, Family: Fabaceae) In this study, 32 women with PCOS were administered with combined application of astragalus polysaccharides and diene-35 for 3 months. Sex hormones, insulin sensitivity and blood lipid were evaluated before and after the therapy. After the treatment, fasting serum insulin levels, LH/FSH ratio was found be reduced and insulin sensitivity index increased significantly. Astragalus polysaccharides plus diene-35 can be effective in improving insulin resistance, high androgen hormone status and lipid metabolism in patients with PCOS and it may be alternative for PCOS [28]

White peony

(Botanical Name: *Paeonia lactiflora*, Family: Paeoniaceae) In the present study, we investigated the in vivo effects of unkei-to (Japanese herbal medicine) and its compounds on the steroid genesis and cytokine secretion in human granulosa cells. Unkei-to stimulate the secretions of 17-betaestradiol and progesterone from highly luteinized granulosa cells obtained from in vitro fertilization patients. Effect of observed due to its key ingredients like *Paeoniae radix*, *Paeonia lactiflora*, *Cinnamomi cortex* and *Cinnamomum cassia*. The various beneficial actions of unkei-to on the ovary may result from a combination of different ingredient herbs with different stimulatory effects on both steroid genesis and the ovulatory process within the ovary, as well as stimulatory effect on the hypothalamus-pituitary axis [29,30].

D-chiro-inositol

Source: breakdown of phytic acids found in vegetables, fruits, legumes, nuts and whole grains. In this study 44 obese women with PCOS were selected for clinical trial. Serum steroids and glucose tolerance tests were carried out before and after the oral administration of 1200 mg of D-chiro-inositol or placebo once daily for six to eight weeks. The serum progesterone concentration was measured weekly to monitor for ovulation. The level of serum free testosterone, plasma triglyceride and blood pressure was found to be decreased and 19 out of the 22 women who received D-chiro-inositol ovulated [31].

Flower Remedies

Flower remedies may be taken on their own, in a prepared combination, or in a mix of your selection. Single essences are sold at what is known as stock strength, meaning that you should dilute them further before taking them. Purchased combinations are ready to take immediately. If you are mixing your own selection, you should fill a glass of water until it is three quarters of

the way full, and then add 3 to 4 drops of a few different flower essences (although it is recommended you use no more than seven). Each dosage should involve 4 to 6 drops on the tongue, taking care to ensure the dropper doesn't touch your mouth. Alternately, you can add a few drops to a glass of water (Table 3) [32].

Ayurvedic Treatment

Female infertility accounts for 35-40 % of overall infertility. Treatment depends upon the specific identifiable cause. Ayurvedic herbal treatment of female infertility is discussed below (Table 4).

Aromatherapy: Aromatherapy can be beneficial in two ways when trying to get pregnant. Firstly, aromatherapy assists in regulating the menstrual cycle and promoting a healthy reproductive system. And secondly, aromatherapy helps you relax; reducing levels of stress and depression, and can even function as an aphrodisiac for you and your partner. In aromatherapy, essential oils are used in order to stimulate relaxation in the muscles

and to relieve tension. Essential oil is highly concentrated plant substances, distilled from roots, seeds, bark and leaves ⁽⁴⁵⁾. They are usually costly because of the tiny amounts of oil present in a plant and because of the difficulties in extracting it. Because essential oils are so concentrated, they should not be applied directly to the skin. Instead, try the following methods.

Acupuncture and Female Infertility

Many women chose acupuncture infertility treatment either on its own or in conjunction with assisted reproductive technology (ART) procedures, such as IVF. Studies have proved the effectiveness of acupuncture for infertility [40]. A 2004 study conducted by the Reproductive Medicine and Fertility Center in Colorado found that 51% of women who underwent both IVF and acupuncture treatment at the same time became pregnant, while only 36% of those who only underwent IVF did. The latter group also had higher rates of miscarriage stillbirth (20%) compared to those women who had received acupuncture (8%) [41].

Table 1. Ovarian Failure Treatment for Female Infertility

History of patients	Fertility drugs may be used to induce ovulation (17)
Elevated Prolactin Hormone Levels	CAT (computerized axial tomography) scans can determine if a benign pituitary tumor is the cause. A drug called bromocriptine can shrink the tumor. Hypothyroidism, if the cause, can be treated with thyroid medication.
Absence of GnRH GnRH replacement	Absence of GnRH GnRH replacement
Premature Ovarian Failure	Treatment is limited to Assisted Reproductive Technology (ART) using donor egg, which is fertilized in the laboratory, and implanted into the uterus of the woman who cannot conceive naturally [20]
Cervical Mucus Problems	Estrogen therapy to stimulate production of mucus that aids the sperm in reaching the egg. ART is another option. Sperm are collected and injected directly into the uterus (intrauterine insemination), bypassing the vagina and the cervix [20]
Pelvic Inflammatory Disease (PID)	The more sexual partners a person has, the more likely that person is to contract a venereal disease. Condoms provide a protective barrier which minimizes risk. Seek medical attention for diagnostic tests and evaluation if you have any symptoms, concerns or fear that you have been exposed. Most bacterial infections can be treated with antibiotics [19]. Scarring and damage can be seen with dye studies, a hysteroscopy (To view the inside of the reproductive organs) and a laparoscope (to view the outside of the reproductive organs). Repairing damage involves microsurgery or laser surgery to remove scar tissue and reconstruct damaged areas [21].
Endometriosis	Drug therapy can shrink the abnormal growths. Surgery can be performed to remove the abnormal endometrial tissue and growths [21].

Table 2. Alternative Herbal Remedies Available for PCOS

Sr no	Common name	Botanical Name & Family	Part Used	Constituent Present	Other use
1	Saraca	<i>Saraca indica</i> Fabaceae	Flower & bark	Tannin & anthocyanin	Uterine tonic
2	Mugwort	<i>Artemisia vulgaris</i> Asteraceae	Leaves & seed oil	Essential oil	Antidote
3	Blue cohosh	<i>Caulophyllum thalictroides</i> Berberidaceae	Roots & Rhizomes	saponins	Female problems
4	Betel nut	<i>Areca Catechu</i> Palmae	Seeds	Alkaloid	Anti parasites

5	Myrrh	<i>Commiphora molmol</i> <i>Burseraceae</i>	Oil	Volatile oil	Laxative, Anti-inflammatory
6	Cumin	<i>Cuminum cyminum</i> <i>Umbeliferae</i>	Fruit	Volatile oil	Digestant
7	Red clover	<i>Trifolium pretense</i> <i>Fabaceae</i>	Flower	Glycoside	Skin problem
8	Sarsaparill	<i>Smilax officinalis</i> <i>Smilacaceae</i>	Rhizome	Resin	Antibiotic
9	Triphala	<i>Embllica Officinalis</i> <i>Terminalia beletica</i> <i>Terminalia chebula</i>	Fruit	Tannin	Astringent
10	Colic root	<i>Dioscorea villosa</i> <i>Dioscoreaceae</i>	Root	Steroidal saponin	Rheumatism
11	Kelp	<i>Nereocystis leutkeana</i> <i>Laminariaceae</i>	Seaweed	Algin	Hormone balance

Table 3. Flower Remedies When Getting Pregnant

She Oak	She oak reduces stress caused by fertility issues and improves hormonal imbalances
Vervain	A relaxing flower remedy that calms feelings of anxiety and hypertension, which can impede fertility
White Chestnut	Another flower remedy helpful in getting pregnant, white chestnut reduces tension, stress and anxiety. Helpful in promoting mental health, white chestnut is particularly helpful in reducing feelings of bitterness and frustration which women who have difficulty getting pregnant often experience in their journey towards pregnancy. Also promotes positive thinking
Wisteria	Promotes feelings of sensuality in the body and promotes calmness
Aspen	Aspen helps reduce feelings of anticipation and anxiety, thereby reducing your levels of stress and helping to promote better overall reproductive health which increases your fertility

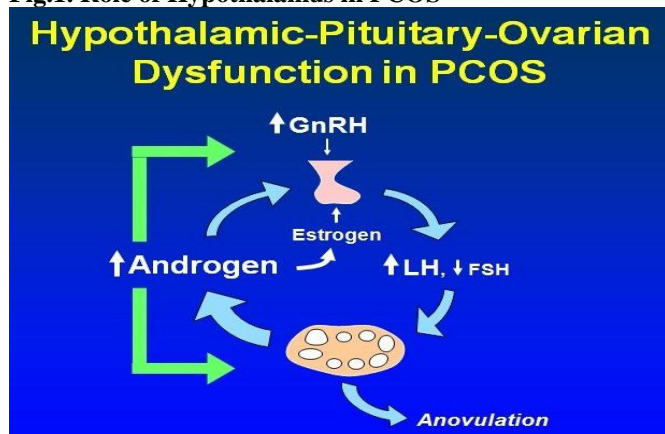
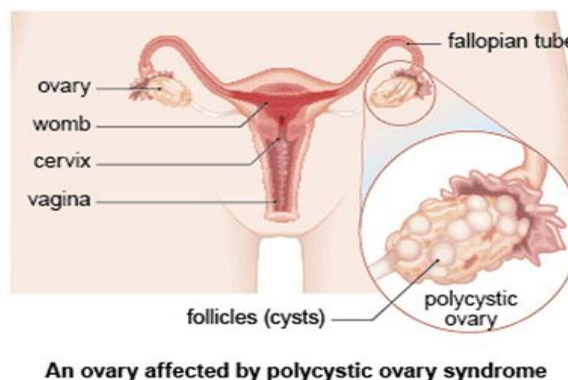
Table 4. Ayurvedic Treatment for Female Infertility

Ovulation disorder	Chandraprabha Vati, Yograj Guggulu, Ashokarishta and Dashmoolarishta. Herbal medicines useful in this disorder are: Ashoka (<i>Saraca indica</i>), Dashmool (Ten Roots), Shatavari (<i>Asparagus racemosus</i>), Aloes (<i>Aloe vera</i>), Guggulu (<i>Commiphora mukul</i>), Hirabol (<i>Commiphora myrrha</i>) and Harmal (<i>Paganum harmala</i>) [33].
Blocked fallopian tubes, adhesions (scar tissue) and pelvic inflammatory disease	Kaishor Guggulu, Triphala Guggulu, Guduchi, Kutki (<i>Picrorrhiza kurroa</i>) and Punarnava can be used in these conditions [34].
Cervical mucus	Vata (<i>Ficus bengalensis</i>), Ashwatha (<i>Ficus religiosa</i>), Udumbara (<i>Ficus glomerata</i>), Plaksha (<i>Ficus infectora</i>), Shirisha (<i>Albizia lebec</i>), Haridra (<i>Curcuma longa</i>), Yashtimadhuk (<i>Glycyrrhiza glabra</i>), Saariva and Manjishtha (<i>Rubia cordifolia</i>).
Women who are underweight or have a small, undeveloped uterus or cervix	Shatavari, Ashwagandha (<i>Withania somnifera</i>), Vidarikand (<i>Pueraria tuberosa</i>), Ksheervidari (<i>Ipomoea digitata</i>), Bala (<i>Sida cordifolia</i>), Samudrashok (<i>Argyria speciosa</i>), Nagbala (<i>Grewia hirsuta</i>), Shrungatak (<i>Trapa natans</i>) and Yashtimadhuk [35]
Some women do conceive, but are unable to retain the pregnancy till full-term	Guduchi, Kantakari (<i>Solanum xanthocarpum</i>), Brihati (<i>Solanum indicum</i>), Gokshur (<i>Tribulus terrestris</i>), Bhrungraj (<i>Eclipta alba</i>), Yashtimadhuk, Pippali (Piper longum), Bharangi (Clerodendrum serriatum), Padmakashtha (<i>Prunus cerasoides</i>), Rasna (<i>Pluchea lanceolata</i>) and Manjishtha [36]
Premature ovarian failure (POF)	Ashoka, Dashmool, Chandraprabha, Shatavari, Guduchi, and Jeevanti (<i>Leptadania reticulata</i>). These medicines can be given in addition to hormone replacement therapy [37]

Table 5. Aromatherapy for Treatment of Female Infertility

Baths	Add 5 to 10 drops of essential oil to a warm bath in order to reduce stress, depression and anxiety. If you are sensitive to essential oils, try diluting them in some base oil or a little milk and allow the oils to disperse before entering the bath [38].
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Oil Burner	Add 3 to 4 drops of essential oils to a container holding water that is heated by a small candle, allowing the aromas to gently fill the air. It is believed that the healing properties of aromatherapy enter the body through the capillaries of the nose [38].
Massage	Dilute the essential oil in a base such as grape seed oil, wheat germ or almond oil; the essential oil should be in the region of 1 to 3 per cent of the quantity of the base. Massage can also be an excellent getting pregnant aphrodisiac and you and your partner can take turns massaging one another. Daily massage can be especially helpful to your reproductive system starting on the final day of your period [39].

Fig.1. Role of Hypothalamus in PCOS**Fig.2. Polycystic Ovary (Stein-Leventhal syndrome Ovary)****CONCLUSION**

Stein-Leventhal syndrome or Polycystic Ovarian Syndrome (PCOS) is one of the most common female endocrine disorders which may leads to Infertility. Herbal drugs have promising role in treatment of PCOS and shows steady effect with minimal side effects. Herbal drugs enhance immunity of the body and also regularize menstrual cycle without fluctuating hormonal level. For regulating menstrual cycle, various poly herbal supplements are being used in India, viz. Evicare syrup capsule and Geri forte tablets (Himalaya healthcare), M₂ Tone Forte syrup (Charak Pharma), Mensta syrup (Dabur India) and Mensonorm capsule (Chirayu Pharma). These

herbal supplements, not only prevent ovarian cysts but also cure them. Herbal supplements may take time to cure PCOS but daily usage may treat the disease from its root. The review has successfully narrated all detail information regarding treatment of female infertility and prevention of recurrent abortions. The increased global warming, UV and cosmic rays, radiations of Silicon Medias, mobiles have generated the impairment of female infertility. Genetical disorder and hormonal imbalances are also can be rectified by drugs, alternatives medicines and physiotherapies. Hence there is effective treatment for female infertility.

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