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CURRENT PERSPECTIVES OF MODERN AND TRADITIONAL MEDICATIONS OF LIFESTYLE GYNECOLOGIC DISORDERS: A REVIEW

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ABSTRACT

Modern healthcare system is well equipped to effectively counter majority of known health problems with minimal side effects. But there are still certain conditions which need special attention. Gynecological disorders affect more than 20% of female population worldwide but many of them are yet to have an effective treatment. Allopathic options such as contraceptives and surgical interventions are reported to have severe side effects which may be fatal. Ayurvedic and therapeutic options, though effective with negligible side effects, still need detailed studies and research before there normalized usage. This review attempts to collect and compile curative options for 3 of the major gynecological disorders *viz.* Polycystic Ovary Syndrome, Endometriosis and Uterine Fibroids intraditional medicinal systems. We have also attempted to find the loopholes which may be taken up for further studies in order to reach stable, dependable and affordable solutions for the above listed disorders.

Keywords: PCOS, Endometriosis, Uterine Fibroids, Gynecological disorders, Traditional Medicine

INTRODUCTION

The modern world is, undoubtedly, making research and technical advancements in the field of healthcare in leaps and bounds. Many health problems and disorders which were once untreatable are now either therapeutically manageable or completely

curable. But with the sedentary lifestyle and unhealthy eating habits, health issues are affecting majority of population. In addition to genetic and environmental factors, gender also has a key role in the kind of ailments that an individual may suffer from.

Gynecologic disorders have long been a taboo and have largely been looked upon since ancient times, especially in the South Asian population. While some of these feminine problems are curable, some are chronic and may prove to be fatal in the long run. Several of these disorders also interfere with fertility. Women have been managing these with local knowledge that has been verbally passed on through generations for centuries now. With the upsurge in exposure to invasive chemicals, which are largely endocrine disruptors, the instances of hormonal disturbances are on a sharp rise. Some of these commonly encountered reproductive and hormonal anomalies include amenorrhea, endometriosis, polycystic ovary syndrome, uterine fibroids, infertility, ovarian cancer, miscarriage, ectopic pregnancy, preterm delivery etc. Most gynecologic disorders have no single medication and treatment approach focuses on the management of symptoms only. Conventional pharmaceutical management of these ailments by means of oral contraceptive pills or through surgical interventions is limited by the prevalence of contraindications in patients, non-effectiveness in some circumstances, side effects and by preferences of women for alternatives to pharmaceutical management. Medical management places strong emphasis on a multidisciplinary approach as pharmaceutical treatments appear to be only moderately effective in treating individual symptoms. Complementary medicine (CM) use by women has increased during the past ten years with rates of use ranging between 26% and 91%, mainly because of ease of usage and minimal or no reported side effects. One of the popular and most preferred types of CM is herbal medicine.

In general, Herb can be defined in commerce as a plant, plant part or plant extract 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 since ages. Herbal products typically involve the use of formulae composed of 10-20 separate herbal ingredients that are prepared either as a boiled decoction, as dried herbal extracts, or taken as pills or capsules. Herbal medicines are known to contain pharmacologically active constituents with

positive physiological effects on female endocrinology and have been associated with reduced incidences of breast cancer, osteoporosis and cardiovascular diseases. Traditional herbal medicines are getting significant attention in global health debates because of their promotive, preventive, curative and rehabilitative effects. The effects of herbal medicines are currently being explored on a large scale for female reproductive disorders. This review has attempted to list the herbal treatment approaches for 3 of the most commonly reported gynecologic disorders *i.e.,*Polycystic Ovary Syndrome, Endometriosis, Uterine Fibroids.

1. POLYCYSTIC OVARY SYNDROME

Polycystic ovary syndrome was initially described by Stein and Leventhal in 1935. It is an extremely prevalent and complex endocrine disorder **[1]**. PCOS associated persistent periods of an ovulation and other endocrine and gynecologic abnormalities account for up to 90% of ovulatory disorders. A study by Hart and Doherty in 2015 reported that infertility is 10 times more common among women with PCOS **[2]**. Using the National Institutes of Health (NIH) 1990 criteria, there are convincing data today to suggest that it affects between 6% and 8% of women worldwide, such that it can be considered one of the most common disorders of humans, and the single most common endocrine abnormality of women of reproductive age **[3]**. It is now considered as a female subtype of the metabolic syndrome and its potential health consequences are a lifelong issue **[4]**. Current evidence indicates that PCOS is a multifactorial polygenic disorder **[3]**.

Diagnosis

There is no universally accepted definition of PCOS. Expert generated diagnostic criteria have proliferated in recent years. There are several diagnostic guidelines for PCOS including those from the Endocrine Society, Androgen Excess and PCOS Society, and multiple regional organizations **[5]**, and although different, all of them rely on combinations of 3 major elements to make the diagnosis: ovulatory dysfunction, hyperandrogenism (clinical or biochemical), and ovarian morphology **[6]**. Other most prominent features of PCOS are decreased HDL levels, obesity and hypertension **[4, 7]**. A study carried by the department of endocrinology and metabolism, AIIMS, shows that about 20-25% of reproductive aged women suffer from PCOS. While 60% of affected women are obese, 35-50% has fatty liver, about 70% have insulin resistance, 60-70% has high level of androgen and 40-60% has glucose intolerance **[8]**. Clinical markers in

females include cutaneous manifestations such as presence of acne, hirsutism and/or male pattern alopecia. Biochemical indications include elevated androgen concentrations in plasma **[1]**. With the advancements in ability to measure hormone concentrations, the diagnostic criteria were revised to include inappropriate gonadotropin secretion and hyperandrogenemia. Development of ultrasonography further shifted attention to ovarian morphology. With recognition of the role of insulin resistance/ hyperinsulinemia in PCOS, the development of methods focused attention on the metabolic abnormalities of the disorder **[3]**. Besides metabolic disorders, physical and psychosocial barriers are commonly observed in women with PCOS, particularly in those with established obesity **[9]**. Genetic background, ethnicity, personal and family history, degree of obesity must all be taken into account for PCOS diagnosis **[4]**.

The Rotterdam criteria (2004), which is currently the most widely accepted, specify that PCOM (Poly Cystic Ovarian Morphology) has at least 12 follicles measuring 2mm to 9mm in the entire ovary or more than 10ml in ovarian size. Transvaginal ultrasound or endometrial biopsy is recommended for PCOS patients who have thickened endometrium, prolonged amenorrhea, unopposed estrogen exposure or abnormal vaginal bleeding **[2, 10, 11]**. Artificial Intelligence (AI) has been reported as the best technology to detect PCOS using segmentation and classification of ultra sound images of ovary **[12]**.

Small antral follicles seen on ultrasound synthesize Serum AMH (Anti Mullerian Hormone) which can be considered an indirect reflection of ovarian reserve. Serum AMH could therefore be used as a surrogate for the AFC (Antral Follicle Count) in the diagnosis of PCOS. Thus elevated serum AMH level is 2–4 folds higher in women with PCOS than in healthy women. The major drawback is that there is a molecular heterogeneity of the circulating AMH level with a non-cleaved biologically inactive form and a cleaved biologically active form. Also, the stability of AMH samples during storage is yet to be studied. Moreover, AMH concentration varies in individuals. Hence it is premature as of now to employ serum AMH level as reliable enough for PCOS diagnosis **[13]**.

Despite developments in technology and diagnostic tools, health care providers continue to struggle with making a diagnosis of PCOS. It has been reported in a survey that more than a third of women spent 2 years seeking a diagnosis to explain their symptoms and saw at least 3 separate

medical providers. Furthermore, only 25% of women were satisfied with the information provided regarding treatment options **[1, 5]**.

Etiology

The etiology of PCOS remains unclear, but it is believed to have epigenetic origins and is a consequence of complex interactions between genetic, environmental and behavioral factors **[1, 4]**. PCOS is an inheritable disorder dependent on the clustering of cases in families. A 5- to 6-fold increase in the occurrence of PCOS among first-degree female relatives of affected patients has been reported when compared with the prevalence of PCOS in general population **[14]**. It is a heterogeneous condition with variable phenotypic expression **[15]**. The disorder can either be morphological (polycystic ovaries) or biochemical (hyperandrogenemia) **[2]**. Clinically, diagnosing a woman as having PCOS implies an increased risk for infertility, dysfunctional bleeding, hypertension, obesity, endometrial carcinoma, dyslipidemia, and possibly cardiovascular disease (CVD) **[3]**. The prevalence of PCOS in type 1 diabetes population has been reported to be about 40.5% while it is extremely common in type 2 diabetes, occurring in 82% of women **[2]**. Many researchers believe that there is a genetic mutation in women with PCOS where insulin can stimulate the ovaries to make androgens **[16]**. In recent years, it has come to light that environmental toxins and pollutants in our food system, like glyphosate, play a role in the development of insulin resistance and PCOS **[16]**. Following are few important causes of PCOS:

Hormonal imbalance: As a consequence of imbalance in female sex hormones, cysts are formed in the ovarian antral follicles. A cyst is a water-filled sac containing the egg that should have been, under normal conditions, discharged for possible fertilization. Formation of cysts therefore blocks ovulation, which results in the disruption of the menstrual cycle, causing 'amenorrhea'. Such multiple cysts in the ovarian follicles due to the hormonal imbalance, characterize PCOS. These water filled follicles, some of which can be as big as 10mm wide, increases the size of the ovary, up to 10 cm wide. Absence of ovulation and menstrual cycle prevents fertilization, and conception, thus pregnancy becomes difficult **[17]**.

Chemical exposure: Exposure to chemicals, by accidental (vehicle exhausts, industrial pollutants, pesticides etc.) or deliberate (cosmetics, household cleaning agents, chemotherapeutics etc.), means are common in current times. Personal care

products such as perfume, sunscreen, hair dye etc., are major culprits behind the rising instances of PCOS **[17]**. Recent studies reported that the expression of some miRNAs was different between PCOS patients and healthy females, which suggest that miRNAs may play important roles in the occurrence and development of PCOS. The possible mechanism for miRNA within the pathophysiology of PCOS has only been sparsely investigated due to complexity of both PCOS and miRNA **[18]**. Strong stimulation in adrenals in childhood, contraceptive pills, stress **[19]** etc. may also be responsible for PCOS.

Effects

PCOS associated endocrine features include elevated LH and reduced FSH concentrations observed in ~60% of PCOS women. High LH level is strongly associated with infertility and miscarriage[15,20]. The high LH/FSH ratio creates a state of hyperandrogenism leading to much of the PCOS symptomology **[1, 16]**. High incidence of impaired glucose tolerance which may approach upto 30–40% in obese populations. Impaired glucose tolerance is further associated with abnormal lipoprotein profile **[21]**. Women with PCOS are characterized by hyperinsulinism i.e., insulin resistance at the level of muscle, adipose tissue and liver, while their ovaries continue to have normal insulin sensitivity. The prevalence of hyperinsulinism is greater in obese than non-obese patients. Overall, between 50% to 70% of women with PCOS have demonstrable insulin resistance **[3, 22]**. Acanthosis nigricans is another condition in which hormonal imbalance in PCOS causes pigmentation. The skin of neck, armpits, thighs and breasts develop light brown or black patches **[1, 17]**. 85-90% women with PCOS have oligomenorrhoea while 30-40% present with amenorrhoea **[23]**. Visceral obesity with its metabolic consequences, that is, insulin resistance, compensatory hyperinsulinemia, dyslipidemia, and hypertension, subsequently leading to cardiovascular diseases is common among women with PCOS **[3, 4]**. Overall obesity is present in approximately 44% of women with PCOS. PCOS patients are also prone to atherosclerosis and arterial stiffness **[24]**. Dyslipidemia are most commonly characterized by high triglycerides and increased low density lipoprotein (LDL) cholesterol with low levels of high-density lipoprotein (HDL)-cholesterol **[25]**. Lipid abnormalities are present in 65-81% of PCOS patients and much higher levels are observed in those with higher insulin resistance **[4]**. Hirsutism is present in approximately 80% of patients and results in thick, course hair growth on the face,

chest and back and sometimes hair loss and male-patterned baldness **[16, 23]**. It appears that aromatase activity is deficient in women with PCOS, and that excess androgens are not being converted into estrogens. Androgens, in fact, inhibit aromatase activity. This aromatase dysfunction creates an imbalance in the estrogen to testosterone ratio, which further exacerbates menstrual cycle irregularities **[18]**. Available data translate into a 9% lifetime risk of developing endometrial cancer in PCOS vs. 3% in the general population **[10]**. An increased risk for ovarian and breast cancer PCOS has also been suggested **[25]**. Unopposed estrogen arising from chronic anovulation may constitute a risk factor for menstrual disorders and ultimately endometrial cancer **[24]**. Elevated LH levels, deficient progesterone secretion, abnormal embryos from atretic oocytes, and an abnormal endometrium have been hypothesized to result in pregnancy loss **[26]**. It is believed that the risk of miscarriage is related to the degree of hyperinsulinemia **[24]**. PCOS patients are also at an increased risk for psychological and behavioral disorders, eating disorders and sexual and relational dysfunction, compromised quality of life, anxiety and depression **[4]**.

Herbal Remedies

Herbal medicines have been lately considered for the treatment of PCOS. Pharmaceutical therapy is effective for the treatment but it may cause several side effects after prolonged usage **[27]**. Often times, herbal medicine is safer than allopathic medicine when addressing chronic health disorders as it works on the root cause of disorder rather than suppressing symptoms alone **[16]**. In a survey, 99% (648 of 657) of women with PCOS expressed their desire for effective treatment alternatives to birth control pills and fertility drugs,and as many as 70% of PCOS patients use medical treatment adjuncts such as complementary medicines **[1, 9]**. Several herbal medicines have been reported to exhibit reproductive endocrineological effect in PCOS, oligo/amenorrhoea and hyperandrogenism **[1]**. Few of them are listed below:

Vitex agnus-castus: Clinical experience has shown that *Vitex agnus castus* is valuable in PCOS because of its action in reducing prolactin, improving menstrual regularity and treatment of infertility **[1]**. Vitex is also postulated to have antiandrogenic properties **[21]**.

Cimicifuga racemosa: *Cimicifuga racemosa* has been reported to lower LH.In a study pregnancy rate was reported at 43.3% in women receiving *Cicimifuga recemosa* along with CC compared to

20.3% for women receiving only clomiphene **[1]**.

Tribulus terrestris: *Tribulus* is an endemic weed to many regions of the world, such as the Mediterranean, China, India, South Africa and Australia and is commonly known as puncture vine. The aerial parts, particularly the leaf, are used for medicinal purposes. Treatment with two doses of *Tribulus terrestris* extracts demonstrated significantly improved ovulation rates for animals compared to controls. Laboratory findings of ovulation induction are supported by the clinical findings of elevated FSH following treatment with *Tribulus terrestris* **[1, 21]**.

Paeonia lactiflora and Glycyrrhiza spp.: *Glycyrrhiza uralensis* alters the morphological features of polycystic ovaries **[1]**. Studies revealed that glycyrrhetinic acid, a constituent of *Glycyrrhiza glabra* significantly decreases testosterone production from the rats' ovaries. *G. glabra* has also been attributed to a reduction in body mass during oral treatment which may be of benefit for overweight women with PCOS.It has been confirmed through pharmacological research that paeoniflorin; a key constituent of *P.lactiflora*significantly decreases testosterone production from the ovaries **[11]**. An animal study found significant reductions in free and total testosterone following exposure to the two-herb combination of *G. uralensis* and *P. lactiflora.* These findings were supported in two clinical trials including women with PCOS and women with hyperandrogenism **[1]**.

Mentha spicata (Spearmint Tea): A 30 day randomized controlled trial was carried out with forty-two volunteers who were given spearmint tea twice a day for a 1-month period and compared with a placebo herbal tea. Free and total testosterone levels and degree of hirsutism were reduced post the 30-day period in the spearmint tea group. LH and FSH were increased. It was demonstrated and confirmed that spearmint has antiandrogenic properties **[19]**.

Linum usitatissimum (Flaxseed*)*: In a study the impact of flaxseed supplementation on hormonal levels in a 31-year-old woman with PCOS was observed. Height, weight measurement and fasting blood samples taken at baseline and 4-month follow-up indicated clinically significant decrease in Body Mass Index (BMI), insulin, total serum testosterone and free serum testosterone levels. The patient also reported a decrease in hirsutism **[19]**.

Aloe barbadensis (Aloe Vera): The efficacy of Aloe vera in a PCOS rat model was checked. The Aloe vera gel formulation (1 ml) dose daily for 45 days restored their

estrus cyclicity, glucose sensitivity, and steroidogenic activity **[19]**.

Cinnamomum verum appears promising in terms of treating insulin resistance and hyperinsulinemia and additionally, to combat some of the longer term CVD consequences **[11]**.

The quality of evidence, as determined by the volume of pre-clinical studies and the methodological quality of clinical trials, was highest for *Vitex agnus-castus*, *Cimicifuga racemosa*and *Cinnamomum cassia*, for which there were laboratory and/or animal studies demonstrating endocrine mechanisms of action consistent with clinical outcomes shown in RCT's. Evidence for *Tribulus terrestris*, *Glycyrrhiza* spp. alone and in combination with *P. lactiflora* and *P.lactiflora* with *Cinnamomum cassia* is limited with only one to two studies found for each herb or herbal combination. Clinical investigations found no adverse effects for herbal medicines **[1]**. Evidence for the use of these herbal medicines is preliminary and in an emergent phase. With the use of ovaryl tablet which contains herbs, PCOS patients showed significant decrease in weight, serum insulin levels and both ovary volume within few days of use. Along with reduced PCOS symptoms, hirsutism, irregularity of periods and ovulation symptoms were significantly decreased with complete treatment of 3 months medication **[23]**. A random controlled trial demonstrated a statistical and clinically significant result for a lifestyle intervention along with addition of a novel herbal combination compared with lifestyle intervention alone. Improvement was reported in PCOS symptomology including a reduction in menstrual, improved anthropometry, reduced LH level, fasting insulin, blood pressure, conception rates and quality of life. The study also showed statistically significant reduction in women's depression, anxiety and stress scores **[9]**.

2. ENDOMETRIOSIS

Endometriosis (EM) is known to be a chronic gynecologic disorder that generally occurs when endometrial tissue grows abnormally and adheres outside of the uterus **[28, 29]**. It is an estrogen-dependent debilitating disorder and is reported in females during childbearing age or adulthood predominantly between the ages of 25–29 years **[30]**. It affects up to 5–10% of women of reproductive age **[31]** out of which frequency of infertility, pain or both is 35-50% **[29]**. About 25-50% of infertile women suffer from endometriosis which is up to 10X more frequent than in the general population (0.5–5%) **[32]**. The most common symptom of endometriosis is pelvic pain, just before and after periods. EM manifests high variability ranging from

minimal superficial lesions to severe disease involving the bowel and bladder **[33]**. It is generally regarded as benign, however, has been linked to a malignant tumor since the lesions can grow, infiltrate and adhere to the adjacent tissues **[29]**. Depending upon the site of implantation, EM can be classified as ovarian EM, peritoneal EM, and deep infiltrating EM **[28]**. It has been reported to exhibit high recurrence rates following treatment **[34]**.

Etiology

The following have been reported to be the most common factors causing endometriosis:

Retrograde menstruation (Sampson's hypothesis): It is the back flow of menstrual blood into a woman's body during her period. The blood, along with it, carries endometrial tissues which deposit in the peritoneal cavity and proliferate until they become endometriotic lesions. This is currently the most widely accepted theory **[29, 31, 34]**.

Coelomic metaplasia: Coelomic epithelium is the common ancestor of endometrial and peritoneal cells, thus allowing transformation of one type of cell into another **[30]** because of chemical irritation or chronic inflammation from refluxed menstrual blood **[29]**.

Vascular and lymphatic spread: Endometrial tissues infiltrate the local blood and lymphatic system from where the vascular blood is transported to distant sites in the body and leads to altered immunosurveillance **[29]**.

Dysregulated immune systems: Compared to healthy women, endometriosis patients have significant upregulation of activated macrophages, T and B cells, inflammatory cytokines, antigens and inhibitory receptors in the peritoneal fluid, stem cell growth factor b (SCGFB), interleukin (IL) 8, human growth factor (HGF) and monocyte chemoattractant protein 1 (MCP1). In addition, downregulation of cytotoxic NK activity and IL13 has been observed. These dysregulated immune cells and their cytokine networks might stimulate the initiation and progression of endometriosis **[31]**.

Inflammatory responses: Altered inflammatory signaling in immune cells release pro-inflammatory cytokines which bind to their receptors in endometriotic lesions and further initiate and establish endometriosis progression. These cytokines significantly reduced apoptosis in eutopic endometrial tissue in patients with endometriosis **[31]**.

Elevated iron level has been reported in the cells and peritoneal fluid of women with endometriosis, inducing deleterious ROS in the peritoneal environment, which enhances the attachment and growth of

retrograde menstrual tissues **[31]**. Connexins (Gap junction proteins), abnormalities of the genital tract,genetic predispositions, hormonal imbalances and hereditymay also be responsible for endometrial lesions **[29, 35].** Endometriosis is usually difficult to be diagnosed and is identified generally when the females start treatment of their infertility **[29, 36]**.

Effects

Most affected by endometriosis are ovaries, uterine ligaments, recto and vesicovaginal septae, pelvic peritoneum, cervix, vagina and labia **[29, 30]**. Most common symptoms are chronic pelvic pain (cellular and neural mechanisms of pelvic pain associated with endometriosis are poorly understood) **[37, 38]** dysmenorrhoea, dyspareunia, and infertility, which all may lead to a reduction in the patient's quality of life **[28]**. Often marked by pain during sex and after sex, during urination and bowel movements **[39]**. Endometriosis may as well interfere with reproduction, ovulatory functions and conception. Additionally, it also deregulatesmRNA trancript encoding protein involved in uterine receptivity and implantation **[29]**. All aspects of IVF (peak E2 concentration, number of oocytes retrieved, fertilization rate, and implantation rate) are affected by the presence of endometriosis **[40]**. Ovarian response is negatively affected. Both oocyte/embryo number and quality have been claimed to be affected by the disease **[32, 40]**. Altered folliculogenesis, reduced quality and cytoplasmic mitochondrial content of oocytes, oocyte/embryo exposure to a hostile inflammatory environment (macrophages, cytokines and vasoactive substances in the peritoneal fluid), anatomical dysfunctions of the tubes and/or ovary are adverse conditions reported due to endometriosis **[32]**. Malignant transformation of endometriosis may occur in up to 1% of women, with the most common site being the ovary **[30]**. Severe endometriosis results in pelvic adhesions and distortion of pelvic anatomy **[40]**.

Herbal Remedies

Herbal products alleviate dysmenorrhoe, shrink endometriotic lesions, promote pregnancy and reduce recurrence. There are several common decoctions used to treat EM in China, including XuefuZhuyu decoction (XZD), Xiaochaihu decoction (XCHD), Qu Yi Kang (QYK), Yi Wei Ning (YWN), YiWei San (YWS), and HuoxueXiaoyi decoction (HXD).A clinical trial reported that XZD could relieve dysmenorrhoea as effectively as Mifepristone tablets, with the total effective rate being 90% and 73% in the XZD group and Mifepristone group, respectively.In another study, a rat model receiving XCHD

treatment, the volume of endometriotic lesion was significantly reduced. Some researchers also showed that XCHD could directly inhibit the growth of the ectopic endometrium in rat models by increasing Fas protein expression and promoting apoptosis in ectopic endometrial tissues [28].Among medicinal anti-endometriosis herbs that inhibit the prostanoid system, *Dahurian angelica* root, licorice root, cinnamon, poria, scutellaria, curcuma and the formulae KBG, YWN and Neiyi have been best studied **[38]**. Reactive oxygen species (ROS) have been suggested to play a role in the pathogenesis of endometriosis. Retrograde menstruation allows transport of pro-oxidant factors, such as heme, iron and apoptotic endometrial cells, which are the inducers of oxidative stress, into the peritoneal cavity of women with endometriosis **[41]**. ROS can promote growth of endometrial stromal cells. Antioxidants, such as vitamin E, reported beneficial effects in an in vitro model of endometrial proliferation **[42]** and anti-inflammatory effects in a rodent model of LPS-induced inflammation leading to increased embryo viability **[43]**. Drugs with antioxidant properties have been developed as possible treatment choices for endometriosis, but conclusive evidence on the benefits of the various modalities is lacking **[38]**.

3. **Uterine Fibroids**

Uterine fibroids, aka myomas, are the most common, non-cancerous uterine growths. These are basically benign monoclonal neoplasms arising from the smooth muscle compartment of uterus in about 20% of women aged above 35 years and are frequently associated with infertility, hypermenorrhea and dysmenorrheal **[44, 45, 46]**. Leiomyoma is the most common benign uterine neoplasm affecting approximately 40% of women over 50 years of age **[47]**. Although most uterine fibroids are asymptomatic, 25% of women have mild to severe symptoms that impact activities of daily living **[48]**.

Etiology

The etiology of uterine fibroids remains elusive, however genetic, hormonal, immunological, and environmental factors may play a role in starting the growth of fibroids, or in continuing that growth **[45]**. Growth is influenced by female gonadal steroids and there is considerable evidence that estrogens and progesterone play a key role for maintenance and growth of uterine leiomyoma **[47]** as the fibroids rarely appear before menarche and regress after menopause **[49]**. Fibroids may grow as a single tumour or in clusters of size varying from one inch to eight inches or more and contain large amount of collagen, fibronectin, and proteoglycan. They may

cause problems due to their size, number, or location. Common symptoms include longer or more frequent menstrual periods, heavy bleeding, menstrual pain and pressure in the lower abdomen **[45]**.

According to the location of growth, they can be categorised as

Submucosal: Grow just underneath the uterine lining.

Intramural: Grow in between the muscles of the uterus.

Subserosal: Grow outside of the uterus **[45]**.

Subserosal or intramural fibroids negatively impact fertility. All fibroids are the leading cause of hysterectomy **[50]**. Fibroids often result in abnormal uterine bleeding and subsequent anemia, pelvic pressure or pain, and reproductive dysfunction **[51]**. Fibroid cells secret high levels of collagen and resist apoptosis. As women delay childbearing, the risk of developing uterine fibroids increases **[48]**.

Herbal Remedies

Literature is available for the use of Traditional Chinese Medicines for the treatment of uterine fibroids. It has been reported that *Herba scutellariae barbatae* (Ban-Zhi-Lian), *Tripterygium wilfordii* (Lie-Gong-Teng) and Gui-Zhi-Fu-Ling-Wan (Cinnamon Twig and Poria Pill) may have the potential to treat uterine fibroids[46].In a meta-analysis, the most commonly prescribed Chinese herbal formula was found to be Gui-Zhi-Fu-Ling Wan (Cinnamon Twig and Poria Pill), followed by Jia-Wei-Xiao-Yao-San (Supplemented Free Wanderer Powder), and Shao-Fu-Zhu-Yu-Tang (Lesser Abdomen Stasis Expelling Decoction). The most prescribed single herb was reportedly San-Leng (*Rhizoma sparganii*), followed by E-Zhu (*Rhizoma curcumae*), and Xiang-Fu (*Rhizoma cyperi*). A recent systemic review and meta-analysis also reported that adjunctive use of Gui-Zhi-Fu Ling-Wan with mifepristone is associated with a greater reduction in fibroid volume and uterine size, compared with mifepristone alone **[46]**. In general, Chinese herbal medicines are used mainly for symptom improvement. However, according to recent studies, the prescribed chinese herbal remedies seemed not only to relieve the symptoms or comorbidities of uterine fibroid, but also treat uterine fibroid itself. But there is lack of large-scale survey on the use of traditional Chinese medicine [TCM) to treat uterine fibroids. It might be of great potential to develop drugs to medically manage uterine fibroid from the formulas or single herbs used in Traditional Chinese Medicine **[45, 46]**.

CONCLUSION

PCOS is evidently a very common condition which represents a major health

burden for women and communities. It remains a syndrome and, as such, no single diagnostic criterion is sufficient for appropriate clinical diagnosis, but improvededucation and awareness could impact diagnosis and treatment. Unfortunately, the medications currently available for the treatment of PCOS are not fully able to deal with all the metabolic consequences and might have adverse effects. The therapeutic management of these metabolic aberrations is evolving to incorporate new treatments resulting from the better understanding of the pathophysiology of the syndrome. Longer, randomized controlled trials, which will address the cardiovascular risk, are needed to establish the benefit and safety of the available treatments on the metabolic aberrations of the PCOS. While there is no full consensus about the exact cause or cure for PCOS, there are ways by which women can manage the syndrome so as to improve their health, reduce symptoms, boost fertility and increase the overall quality of their life. Preliminary studies show that herbal treatment appears to be well tolerated by PCOS patients with no reported side effects. Herbal supplements may take longer time to cure PCOS, but daily usage may treat the disease from its root. Further research into the use of phytotherapy in the treatment of women with PCOS is both justified and necessary to substantiate the preliminary results. Successful lifestyle modifications may have far reaching beneficial effects for PCOS patients. Most studies have focused on only one lifestyle-related change, such as exercise, as opposed to a more synergistic approach wherein diet, exercise, and stress reduction are combined. At present, the integrated approach with nutritionally adequate diet, Ayurvedic support, vitamins, minerals, moderate exercise and de-stressing and medical assistance offering minimum side effects seems to be the most promising way of managing PCOS.

Further studies in endometriosis may be directed towards understanding its molecular etiology and offering new molecular therapeutic targets to improve the specificity of endometriosis therapy and reduce side effects of current treatments. Dysregulation of the immune system, apoptosis and oxidative stress are closely associated with the progression of endometriosis. Epigenetic changes caused by nutrition and environmental variables or genetic changes might be potential factors that can initiate endometriosis.

Drug therapies prescribed for uterine fibroids are either short-lived or have significant side effects. Current clinical needs in case of uterine fibroids include an

effective prevention strategy as far as possible, improving early detection, slowing the growth of fibroids, development of better treatment modalities and reducing recurrences after treatment. A better understanding of the molecular basis for fibroid development and myometrial proliferation will greatly aid in the development of additional nonsurgical therapeutic interventions. There is no conclusive evidence for the use of herbal preparations for treatment of uterine fibroids due to a limited number of trials conducted for individual herbal preparations. Clinically relevant outcomes, such as symptoms, quality of life, infertility, and anaemia, should be addressed before a potentially promising herbal preparation can be considered. Furthermore, future trials should also pay more attention to the adverse effects of herbal medicines, especially for long-term use.

DISCUSSION

From the available data, it is clear that the pharmaceutical approaches at present are not potent enough for the management of gynaecologic disorders. The management of symptoms provides temporary relief, but the recurrence rate is considerably high post cessation of pharmacologic therapies. In addition, many patients have also reported contra indications and adverse effects of drugs if used for extended periods. Surgical interventions are the ultimate resort. But surgery is not feasible in all cases as it may cause permanent loss of fertility, the patient may not be physiologically sound, economic condition may not allow and there may be severe complications later in life. Overall, it is necessary and justified to look for alternate treatment approaches for female reproductive disorders. Herbal therapies are proving to be a very effective treatment option because they are usually quite tender on the body and have fewer side effects than medication **[8]**. Benefit of herbal therapy compared to conventional therapy is that it is safe with lesser or no side effects and presence of multiple active constituents in medicinal herbs altogether provides a potentiating effect **[23]**. In a recent meta-analysis involving more than 4200 women, it was reported that Chinese herbal medicine (CHM) taken over 3—6 months is more effective in the treatment of female infertility than Western medical (WM) drug treatment, achieving an average 60% pregnancy rate with CHM compared to 33% with WM. Trials included women with PCOS, endometriosis, fallopian tube blockage, anovulation, or unexplained infertility. Benefits of the inherent synergism within herbal products are enhanced efficacy and reduced toxicity

[52]. However, there's still a long way to traverse before herbal medications are standardized. Several biochemically active compounds present in herbal preparations complicate the investigation of their mechanisms of actions. Some interacting substances might compete or increase toxicity. Another major difficulty in studying the clinical effects of herbal combinations with respect to evidence-based standards is that the composition of herbal formulae is individualized for each patient according to the different disorders **[38]**. Hence, the potential for both positive and negative interactions necessitates careful study and validations of existing and new herbal therapies for these common conditions **[1, 38]**. Further, there are hardly any studies comparing the effectiveness of herbal medicines and pharmaceutics, which is another important research aspect for proving the potential of herbal products. It is hoped that medicinal herbs or combinations of medicinal herbs and drugs will promote health and wellbeing, while minimizing toxicities and side effects **[38]**. Herbal therapy has lately reached a turning point such that it is fighting to be recognised as a science-a particular field with its own identity. It has become necessary to show that herbal therapy can match other fields of medicine in the thoroughness of its scientific work and its practical use **[53]**.

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