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Management of Polycystic Ovarian Syndrome (Keesa-e-Khusyatur Rehm): Unani Perspective

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ABSTRACT

The polycystic ovarian syndrome (PCOS) is the most common endocrine disorder that affects between 10-15% of women during their reproductive age. Its prevalence is 6.5% to 8%, using biochemical and/or clinical evidence, and ultrasound-based studies have reported a prevalence of 20% or more. Anovulation is hallmark of PCOS which is the leading cause of infertility in this syndrome with a prevalence of 68%. PCOS is a heterogeneous disorder. It was originally described by Stein and Leventhal in 1935 as a clinical triad of hyperandrogenism, anovulation and obesity in women with enlarged polycystic ovaries. Women with PCOS are at increased risk of reproductive problems including infertility, endometrial cancer, late menopause and also metabolic aberrations including insulin resistance, type 2 diabetes mellitus, dyslipidemia and cardiovascular diseases. In Unani System of medicine, the disease has not been defined under the term of PCOS; as disease has been categorized recently just a century before. The description of the disease has been described vividly by various Unani physicians under the headings of *ehtebase tams* and *uqr* According to Hippocrates the main cause of the disease is impairment of humors *(Akhlat).* PCOS cater to different symptoms, effective treatment to manage PCOS is a challenge.The best known treatment of PCOS at present is by using allopathic medicines such as clomiphene citrate, metformin, tamoxifene and troglitazone. All these drugs have mild to severe side effects including hot flushes, arthritis, joint or muscle pain and psychological side effects such as irritability, mood swings, depression and bloating. So there is a need for developing a regimen to offer cheap and best treatment for this disease.Unani system of medicine is the oldest system that prevails till dates with its effective remedies derived from plants, animals and mineral sources. There are various single and compound drugs to cure different disorders of the human body. The causes of infertility in female due to obesity and PCOS as described by modern medicine are very much similar to the causes and features of *uqr* in Unani medicine, but the cellular and hormonal concept in relation to this disorder is recent. The drugs which correct *ehtebase tams*, *uqr* and *sue mizaj barid* are generally found to be useful in PCOS, but their efficacy has not been validated scientifically

Keywords: Unani Medicine; PCOS; *Keesa-e-Khusyatur Rehm*

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INTRODUCTION

Polycystic ovary syndrome (PCOS), also called hyperandrogenic anovulation (HA),[1] or Stein-Leventhal syndrome,[2] is one of the most common endocrine disorders among women. There is evidence that it is largely a genetic disease.[3,4,5] Others say it is generally a metabolic dysfunction, since it is reversible.

The condition was first described in 1935 by American gynecologists Irving F. Stein, Sr. and Michael L. Leventhal, from whom its original name of *Stein-Leventhal syndrome* is taken.[6,8]The earliest published description of a person with what is now recognized as PCOS was in 1721 in Italy.[7] Cyst-related changes to the ovaries were described in 1844.[7]

Two definitions are commonly used:

NIH

In 1990 a consensus workshop sponsored by the NIH/NICHD suggested that a person has PCOS if she has all of the following:[8]

1. oligoovulation
2. signs of androgen excess (clinical or biochemical)
3. exclusion of other disorders that can result in menstrual irregularity and hyperandrogenism

Rotterdam

In 2003 a consensus workshop sponsored by ESHRE/ASRM in Rotterdam indicated PCOS to be present if any 2 out of 3 criteria are met[9]

1. oligoovulation and/or anovulation
2. excess androgen activity
3. polycystic ovaries (by gynecologic ultrasound)
4. Other entities are excluded that would cause these.[10]

PCOS produces symptoms in approximately 5% to 10% of women of reproductive age (approximately 12 to 45 years old). It is thought to be one of the leading causes of female subfertility[11,12,13] and the most frequent endocrine problem in women of reproductive age.[14] Finding that the ovaries appear polycystic on ultrasound is common, but it is not an absolute requirement in all definitions of the disorder.

Epidemiology

The prevalence of PCOS depends on the choice of diagnostic criteria. The World Health Organization estimates that it affects 116 million women worldwide as of 2010 (3.4% of

women).[2] One community-based prevalence study using the Rotterdam criteria found that about 18% of women had PCOS, and that 70% of them were previously undiagnosed.[14]

Ultrasonographic findings of polycystic ovaries are found in 8-25% of normal women.[21]14% women on oral contraceptives are found to have polycystic ovaries.[21]

Pathogenesis

- ❖ Polycystic ovaries develop when the ovaries are stimulated to produce excessive amounts of male hormones (androgens), in particular testosterone, by either one or a combination of the following (almost certainly combined with genetic susceptibility[21]
- the release of excessive luteinizing hormone (LH) by the anterior pituitary gland
- through high levels of insulin in the blood (hyperinsulinaemia) in women whose ovaries are sensitive to this stimulus[16]

The syndrome acquired its most widely used name due to the common sign on ultrasound examination of multiple (poly) ovarian cysts. These "cysts" are actually immature follicles not cysts. The follicles have developed from primordial follicles, but the development has stopped ("arrested") at an early antral stage due to the disturbed ovarian function. The follicles may be oriented along the ovarian periphery, appearing as a 'string of pearls' on ultrasound examination.

- ❖ Women with PCOS experience an increased frequency of hypothalamic GnRH pulses, which in turn results in an increase in the LH/FSH ratio.[15]
- ❖ A majority of people with PCOS have insulin resistance and/or are obese. Their elevated insulin levels contribute to or cause the abnormalities seen in the hypothalamic-pituitary-ovarian axis that lead to PCOS. Hyperinsulinemia increases GnRH pulse frequency, LH over FSH dominance, increased ovarian androgen production,[16] decreased follicular maturation, and decreased SHBG binding; all these steps contribute to the development of PCOS. Insulin resistance is a common finding among women with a normal weight as well as overweight women.[14]
- ❖ In many cases, PCOS is characterized by a complex positive feedback loop of insulin resistance and hyperandrogenism. In most cases, it cannot be determined which (if any) of those two should be regarded causative. Experimental treatment with either antiandrogens or insulin-sensitizing agents improves both hyperandrogenism and insulin resistance.
- ❖ Adipose tissue possesses aromatase, an enzyme that converts androstenedione to estrone and testosterone to estradiol. The excess of adipose tissue in obese women creates the

paradox of having both excess androgens (which are responsible for hirsutism and virilization) and estrogens (which inhibits FSH via negative feedback).[22]

- ❖ PCOS may be associated with chronic inflammation,[16]with several investigators correlating inflammatory mediators with anovulation and other PCOS symptoms.[23] Similarly, there seems to be a relation between PCOS and increased level of oxidative stress[24]
- ❖ It has previously been suggested that the excessive androgen production in PCOS could be caused by a decreased serum level of IGFBP-1, in turn increasing the level of free IGF-I, which stimulates ovarian androgen production, but recent data concludes this mechanism to be unlikely.[25]
- ❖ PCOS has also been associated with a specific FMR1 sub-genotype. The research suggests that women with *heterozygous-normal/low* FMR1 have polycystic-like symptoms of excessive follicle-activity and hyperactive ovarian function.[26]

Signs and symptoms

Common symptoms of PCOS include the following:

- ❖ Menstrual disorders: PCOS mostly produces oligomenorrhea (few menstrual periods) or amenorrhea (no menstrual periods), but other types of menstrual disorders may also occur.[14][16]
- ❖ Infertility:[16] This generally results directly from chronic anovulation (lack of ovulation).[14
- ❖ High levels of masculinizing hormones: The most common signs are acne and hirsutism (male pattern of hair growth), but it may produce hypermenorrhea (heavy and prolonged menstrual periods), androgenic alopecia (increase hair thinning or diffuse hair loss), or other symptoms.[14,17] Approximately three-quarters of people with PCOS (by the diagnostic criteria of NIH/NICHD 1990) have evidence of hyperandrogenemia.[18]
- ❖ Metabolic syndrome:[16] This appears as a tendency towards central obesity and other symptoms associated with insulin resistance.[14] Serum insulin, insulin resistance, and homocysteine levels are higher in women with PCOS.[19]

Diagnostic Criteria

- History-taking, specifically for menstrual pattern, obesity, hirsutism, and the absence of breast development. A clinical prediction rule found that these four questions can diagnose PCOS with a sensitivity of 77.1% (95% confidence interval [CI] 62.7%–88.0%) and a specificity of 93.8% (95% CI 82.8%–98.7%).[27]

- Gynecologic ultrasonography, specifically looking for small ovarian follicles. These are believed to be the result of disturbed ovarian function with failed ovulation, reflected by the infrequent or absent menstruation that is typical of the condition. In a normal menstrual cycle, one egg is released from a dominant follicle – in essence, a cyst that bursts to release the egg. After ovulation, the follicle remnant is transformed into a progesterone-producing corpus luteum, which shrinks and disappears after approximately 12–14 days. In PCOS, there is a so-called "follicular arrest"; i.e., several follicles develop to a size of 5–7 mm, but not further. No single follicle reaches the preovulatory size (16 mm or more). According to the Rotterdam criteria, 12 or more small follicles should be seen in an ovary on ultrasound examination[8] More recent research suggests that there should be at least 25 follicles in an ovary to designate it as having polycystic ovarian morphology (PCOM) in women aged 18–35 years.[28] The follicles may be oriented in the periphery, giving the appearance of a 'string of pearls'.[29] If a high resolution transvaginal ultrasonography machine is not available, an ovarian volume of at least 10 ml is regarded as an acceptable definition of having polycystic ovarian morphology instead of follicle count.[28]
- Laparoscopic examination may reveal a thickened, smooth, pearl-white outer surface of the ovary.
- (Serum (blood) levels of androgens (male hormones), including androstenedione and testosterone may be elevated.[14] Dehydroepiandrosterone sulfate levels above 700-800 µg/dL are highly suggestive of adrenal dysfunction because DHEA-S is made exclusively by the adrenal glands.[30,31] The free testosterone level is thought to be the best measure,[31] with ~60% of PCOS patients demonstrating supranormal levels.[16] The Free androgen index (FAI) of the ratio of testosterone to sex hormone-binding globulin (SHBG) is high[14,31] and is meant to be a predictor of free testosterone, but is a poor parameter for this and is no better than testosterone alone as a marker for PCOS,[32] possibly because FAI is correlated with the degree of obesity.[33]

❖ Some other blood tests are suggestive but not diagnostic. The ratio of LH (Luteinizing hormone) to FSH (Follicle-stimulating hormone), when measured in international units, is elevated in women with PCOS. Common cut-offs to designate abnormally high LH/FSH ratios are 2:1[34] or 3:1[31] as tested on Day 3 of the menstrual cycle. The pattern is not very specific and a ratio of 2:1 or higher was present in less than 50% of women with

PCOS in one study.[34] There are often low levels of sex hormone-binding globulin,[31] in particular among obese or overweight women.

- ❖ Anti-Müllerian hormone (AMH) is increased in PCOS, and may become part of its diagnostic criteria.[35,36]

Associated conditions

- Fasting biochemical screen and lipid profile[31]
- 2-Hour oral glucose tolerance test (GTT) in women with risk factors (obesity, family history, history of gestational diabetes)[14]may indicate impaired glucose tolerance (insulin resistance) in 15–33% of women with PCOS.[31] Insulin resistance can be observed in both normal weight and overweight people, although it is more common in the latter (and in those matching the stricter NIH criteria for diagnosis); 50–80% of people with PCOS may have insulin resistance at some level.[14]
- Fasting insulin level or GTT with insulin levels (also called IGTT). Elevated insulin levels have been helpful to predict response to medication and may indicate women needing higher dosages of metformin or the use of a second medication to significantly lower insulin levels. Elevated blood sugar and insulin values do not predict who responds to an insulin-lowering medication, low-glycemic diet, and exercise. Many women with normal levels may benefit from combination therapy. A hypoglycemic response in which the two-hour insulin level is higher and the blood sugar lower than fasting is consistent with insulin resistance.
- Glucose tolerance testing (GTT) instead of fasting glucose can increase diagnosis of increased glucose tolerance and frank diabetes among people with PCOS according to a prospective controlled trial.[37] While fasting glucose levels may remain within normal limits, oral glucose tests revealed that up to 38% of asymptomatic women with PCOS (versus 8.5% in the general population) actually had impaired glucose tolerance, 7.5% of those with frank diabetes according to ADA guidelines.[37]

Differential diagnosis:

- ➢ Hypothyroidism
- ➢ Congenital adrenal hyperplasia (21-hydroxylase deficiency)
- ➢ Cushing's syndrome.
- ➢ Hyperprolactinemia.
- ➢ Androgen secreting neoplasms.
- ➢ Other pituitary or adrenal disorders, should be investigated.[10][14][31]

Unani Aspect:

Female sub fertility is a multifactor disease process with a number of potential contributing causes. Considering the majority of female sub fertility cases are due to anovulatory cycles. Among the anovulatory cycles 75% of the female are associated with Polycystic Ovarian Syndrom (PCOS) [38] . It is a very heterogeneous syndrome both in its clinical presentation and laboratory manifestations. The majority of the women with anovulation due to PCOS have menstrual irregularities, such as Oligomenorrhoea (*Qillat e Tams)* or Amenorrhea *(Ihtibas e Tams)* associated with obesity and clinical or / and bio – chemical evidence of hyperandrogenism. Women with PCOS often have elevated LH level are at higher risk for developing infertility, endometrial carcinoma and a number of metabolic disorders, including insulin resistance, diabetes, hypertension and cardiovascular diseases. [39]

In Unani System of medicine, the disease has not been defined under the term of PCOS; as disease has been categorized recently just a century before. The description of the disease has been described vividly by various Unani physicians under the headings of *ehtebase tams* and *uqr* According to Hippocrates the main cause of the disease is impairment of humors *(Akhlat). Ehtebase Tams* is caused by the domination of *Khilte balgham* which increase the viscosity. Ibn Sina and Majusi stated one of the causes of *ehtebase tams* is *sue mizaj barid* of *rehm* and *samne mufrat* (Obesity). Due to obesity narrowing of the lumen of blood vessels develops and reduces blood circulation and *sue mizaj barid* causes increase in the viscosity of the humours. The Unani physicians described various diseases in this category, such as *qillate tams, ehtebase tams, uqr*. Since PCOS is manifested with symptoms of amenorrhea, infertility, obesity and hirsutism, various descriptions related to the above conditions are found in claimed Unani literature in the description of *Sue mizaj mukhtalif* of *quwate tauleede mani* in women; mainly *sue mizaj barid* causes *uqr* by *toole ehtebase mani* (Chronic anovulation).[40]Further *Jalinoos* says women become amenorrheic if her *mizaj* transformed towards masculinity and develops the features like male pattern hair growth, hoarseness of voice etc.[41] The causes of infertility in female due to obesity and PCOS as described by modern medicine are very much similar to the causes and features of *uqr* in Unani medicine, but the cellular and hormonal concept in relation to this disorder is recent. The drugs which correct *ehtebase tams, uqr* and *sue mizaj barid* are generally found to be useful in PCOS, but their efficacy has not been validated scientifically.

Hirsutism is mentioned in the classical Unani literature as a complication of prolonged amenorrhoea associated with other masculine features, like hoarseness of voice, male body contour,

acne and clitoromegaly [42] Hippocrates (Buqrat460-370 BC) first documented the affiliation of excess facial and body hair (hirsutism) in females with prolonged amenorrhoea, obesity and infertility. Similar observations were reported by Galen (Jalinoos130-200 AD) [43] Rhazes(Muhammad IbnZakariyaRazi865-925 AD) recorded combination of signs conjoined with menstrual irregularities (oligomenorrhoea, amenorrhoea and menorrhagia) including hirsutism, obesity, acne, hoarseness of voice and infertility, which are suggestive of polycystic ovarian disease and hyperandrogenism.[43] Rhazes recommended regular induction of menstruation as one of treatment modality applied for hirsutism[44]. He has also given a line of management for hirsutism based on correction of temperament and menstrual irregularity by use of emmenagogue single herbs or compound formulations and local application of herbs to reduce severity of hair growth. [44]

The pathophysiology of hirsutism was explained by Avicenna (IbnSina980-1037AD) and Zayn al-Din Gorgani (Ismail Jurjani1041-1136 AD). Alteration of normal temperament of female was considered as central dogma for hirsutism. It was said that persistence of amenorrhoea for a long duration causes alterations in internal environment of female body and status of equilibrium is disturbed, leading to formation of some unwanted material which is being excreted through skin pores and participate in the formation of thick hair over the body. It was observed by these physicians that development of masculine features are more common in obese females with robust body and broad prominent blood vessels, because obese women have almost similar temperament as males [42, 45]

Obesity comes from a Latin word ‘obedere’, to devour and in English means very fat. In Unani medicine obesity is termed as *Siman Mufrit* means excessive fat and *farbahi* (Persian word) means *Motapa* (obese) [46.] First it was *Buqrat* (420 BC) who gave detailed description of obesity including its complications, prevention and management in his famous book “*Fasoole Buqratia”. Rofus* (98-171 AD) in his book *Tahzeel Sameen* (treating obesity) describes that obese people are more prone to diseases as they have lack of *Khoon Saleh* (mature blood) and have excess amount of *Khilte Bhalgam*.

MANAGEMENT

Management of women with PCOS depends on the symptoms. These could be ovulatory dysfunction-related infertility, menstrual disorders, or androgen-related symptoms.

Weight reduction

There is some evidence that PCOS-related hyperandrogenism causes central obesity with a high waist/hip ratio independent of the body mass index (BMI). It is well established that obesity is

associated with anovulation, miscarriage, or late pregnancy complications (such as pre-eclampsia and gestational diabetes). Obesity is observed in 35%–60% of women with PCOS and is related to lack of or delayed response to different treatments such as clomiphene citrate (CC), gonadotropins, and surgical treatment of diathermy via laparoscopy.

Weight loss improves the endocrine profile and increases the likelihood of ovulation and pregnancy. Normalization of the menstrual cycles and ovulation could occur with modest weight loss as little as 5% of the initial weight. Weight loss can improve not only circulating androgen and glucose levels but also ovulation and pregnancy rates in obese women with PCOS; however, weight loss is only recommended for those who are overweight with a BMI > 25–27 kg/m^2. The treatment of obesity includes modifications in lifestyle (diet and exercise) and medical and surgical treatment. All these treatments must be performed during the preconception period and not jointly with reproduction therapies.

Diet

Diets recommended for obese PCOS patients are low in calories with a reduced carbohydrate intake, and any form of these diets can produce the 5%–10% loss necessary to re-establish ovarian function in these patients. In 2005, Reaven suggested that low-fat diets produce a decrease in hyperinsulinemia, which improves metabolic effects.

Exercise

Several studies have attempted to establish the role of exercise in the treatment of obese PCOS patients. None found significant differences when different diets, associated or not with exercise, were compared, although a longer weight loss maintenance time did appear to be associated in these patients. An increase in physical activity is recommended for PCOS patients, although this often presents limitations. A knowledge gap exists regarding the optimal type, duration, and frequency of exercise.

Bariatric surgery

Recently, bariatric surgery has been advocated as a strategy for weight loss in the morbidly obese. In addition, if spontaneous weight loss cannot be achieved with diet and exercise, bariatric surgery can be offered. Two primary approaches, restrictive and combined restrictive, and malabsorptive procedures, adjustable gastric banding, and the Roux-en-Y gastric bypass, are commonly performed. Not surprisingly, in 17 women with PCOS and a mean BMI of 50.7 kg/m^2, bariatric surgery resulted in an average loss of 41 ± 9 kg in 12 months and improvements in ovulation, insulin resistance, hyperandrogenism, and hirsutism. In a group of 12 PCOS patients available for follow-up after bariatric surgery for morbid obesity, regular cycles were

restored in all. Of note, women who have had bariatric surgery are at increased risk for nutritional deficiencies, including protein, iron, vitamin B_{12}, folate, vitamin D, and calcium; however, no consensus exists regarding optimal nutritional screening and supplementation.

Ovulation induction

In PCOS, anovulation relates to low FSH concentrations and the arrest of antral follicle growth in the final stages of maturation. Excess LH, androgens, and insulin may individually or collectively play a direct or indirect role in this process, augmenting steroidogenesis but arresting follicular growth. For many women, anovulatory infertility is the presenting complaint. Medications and other options available for the induction of ovulation are reviewed in the following sections.

Clomiphene Citrate

CC constitutes one of the first-line treatments for ovulation induction in these patients, as it is economical, is straightforward, has few adverse effects, and requires little monitoring. CC is an estrogen receptor antagonist that interferes with negative feedback of the estrogen-signaling pathway, resulting in increased availability of FSH. Increased FSH leads to follicular growth, followed by an LH surge and ovulation. CC is indicated in patients with PCOS and anovulation with normal FSH levels, but it has certain limitations in patients with a BMI > 30 and advanced age. Legro et al found significant differences in pregnancy rates in patients with a BMI > 30 compared with those with a BMI < 30.

Doses of 50–150 mg are administered for 5 days, starting on days 3 or 5 of a progestin-induced or spontaneous cycle. CC produces ovulation in 75%–80% of PCOS patients, although when the gestation rate is assessed, it nears 22% per ovulation cycle. These differences in results are attributed to the antiestrogenic effects of CC, mainly on the endometrium and the cervical mucus. The live birth rate following 6 months of clomiphene ranged from 20% to 40%. Furthermore, the majority of pregnancies occurred within the first six ovulatory cycles following the initiation of treatment. Multiple pregnancy rates are under 10%, and hyperstimulation syndrome is rare. Tamoxifen is another oral ovulatory agent that is similar to CC in its mechanism of action, but it lacks its antiestrogenic effect on the cervix and endometrium. It can be used as an alternative to CC in case of CC resistance or failure.

Metformin

Metformin is a biguanide currently used as an oral antihyperglycemic agent and is approved by the US Food and Drug Administration (FDA) to manage type 2 diabetes mellitus. The use of metformin is associated with increased menstrual cyclicity, improved ovulation, and a reduction

in circulating androgen levels. Metabolic benefits are enhanced in the presence of weight loss, and weight loss itself may be enhanced in the presence of metformin. Its primary clinical action is to inhibit hepatic glucose production, although it also decreases intestinal glucose uptake and increases insulin sensitivity in peripheral tissues. Metformin likely plays its role in improving ovulation induction in women with PCOS through a variety of actions, including reducing insulin levels and altering the effect of insulin on ovarian androgen biosynthesis, theca cell proliferation, and endometrial growth. In addition, potentially through a direct effect, it inhibits ovarian gluconeogenesis and thus reduces ovarian androgen production.

Several dose regimens have been proposed. In order to increase patient tolerance, metformin is started at 500 mg daily with food. After 1 week, the dose is increased to 1000 mg for another week and then to 1500 mg daily. The target dose is 1500–2550 mg/day (500 or 850 mg three times daily). Clinical response is usually seen at the dose of 1000 mg daily. It appears that some PCOS patients who do not respond to metformin at a dose of 1500 mg daily will respond favorably to 2000 mg daily. The most common side effects of metformin are nausea and diarrhea. Lactic acidosis has been described mainly in patients with renal impairment, congestive heart failure, and sepsis. Traditionally, oral hypoglycemic agents have been regarded as teratogenic, and their use is contraindicated in pregnancy. However, an increasing amount of data supports their safety when used throughout the pregnancy. Glueck et al reported no major birth defects and no effect on motor or social development of infants at 3 and 6 months of age. Compared with the control group of women who did not receive metformin, the incidence of gestational diabetes in the treated group was significantly lower.

To define the exact role of metformin in ovulation induction, it is crucial to distinguish two different indications. In naive PCOS, metformin, as compared with placebo, has been shown to improve ovulation rates, but metformin did not exert significant advantage over CC with respect to cumulative ovulation, pregnancy, or live birth rates. The combined approach of metformin plus CC is not better than CC or metformin monotherapy in naive PCOS. In CC-resistant patients, metformin has no benefit over placebo in ovulation, pregnancy, and live birth rates as a single agent, but the combination of metformin and CC significantly improved ovulation and pregnancy rates when compared with CC alone. However, combined therapy did not improve the odds of live birth. Metformin pretreatment improves the efficacy of CC in PCOS patients with CC resistance. insulin-sensitizing drug that has been shown to improve ovulation and increase pregnancy rates. However, due to its hepatotoxic effect, it has been withdrawn from the market. Another drug in the same category, rosiglitazone (8 mg/day), has been shown to enhance

both spontaneous and clomiphene-induced ovulation in women with PCOS with a mean BMI of 35.5–38.5 kg/m^2. Pioglitazone appears to be effective as well; however, the study is still limited. Although both rosiglitazone and pioglitazone have little short-term risk, fetal safety has not been established (pregnancy category C of the US FDA guidelines). If used, they should be discontinued as soon as pregnancy has been established. Recently, Tang et al updated the Cochrane review about insulin-sensitizing drugs (metformin, rosiglitazone, pioglitazone, D-chiro-inositol) for women with PCOS, oligo/amenorrhea, and subfertility and concluded that metformin is still of benefit in improving clinical pregnancy and ovulation rates. However, there is no evidence that metformin improves live birth rates whether it is used alone or in combination with clomiphene, or when compared with clomiphene. Therefore, the use of metformin in improving reproductive outcomes in women with PCOS appears to be limited.

Aromatase inhibitors

Selective aromatase inhibitors such as anastrozole and letrozole are promising new ovulation-inducing agents. They are reversible and highly potent. Unlike CC, which has a half-life of 5–7 days, the mean half-life of anastrozole and letrozole is ~45 h only. To date, letrozole has been studied much more extensively than anastrozole. Letrozole was introduced as an assisted reproduction treatment following the appearance of multiple adverse effects of CC, CC's scant therapeutic success, and the complexity of gonadotropin treatment. Letrozole inhibits estrogen production in the hypothalamus–pituitary axis, which implies an increase in gonadotropin-releasing hormone (GnRH) and FSH. It is believed that there exists a relative decrease in aromatase in women with PCOS, which reduces the production of follicles responsible for efficacious ovulation. To use this relative deficit, aromatase inhibitors were considered in order to provoke ovulation, because their selective action of blocking the peripheral passage of androgens to estrogens reduces the quantity of estrogens, thereby producing positive feedback in the pituitary, increasing FSH, and optimizing ovulation. The advantage of letrozole is that it avoids peripheral antiestrogenic effects on the endometrium while stimulating monofollicular growth. Letrozole at 2.5–5 mg is administered for 5 days and may be accompanied by FSH (at the normal doses for PCOS patients) and human chorionic gonadotropin (hCG; 10,000 IU) when the follicle diameter reaches 18 mm in order to program the ovulation. However, in a prospective randomized trial comparing letrozole with clomiphene, pregnancy rates were similar. Although Novartis Pharmaceuticals (Basel, Switzerland) has warned against the use of letrozole for ovulation induction (owing to possible teratogenicity), a comparison with clomiphene did not demonstrate increased rates of major or minor malformations.

Glucocorticoids

Glucocorticoids such as prednisone and dexamethasone have been used to induce ovulation. Elnashar et al demonstrated that induction of ovulation by adding dexamethasone (high dose, short course) to CC in CC-resistant PCOS with normal DHEAS is associated with no adverse antiestrogenic effect on the endometrium and higher ovulation and pregnancy rates in a significant number of patients.

In PCOS patients with high adrenal androgen, low-dose dexamethasone (0.25–0.5 mg) at bedtime can be used. In a study of 230 women with PCOS who failed to ovulate with 200 mg of CC for 5 days, addition of 2 mg of dexamethasone from days 5–14 is associated with a higher ovulation rate and cumulative pregnancy rate. Enthusiasm for their use is dampened, however, by their potential adverse effects on insulin sensitivity; therefore, prolonged use should be discouraged.

Gonadotropins

The second possible line of therapy after resistance to CC has been demonstrated in women with PCOS is exogenous gonadotropins. The mechanism of action of gonadotropins is to induce ovulation, maintain and provoke optimum follicle growth via the controlled administration of FSH, and achieve a follicle capable of being fertilized. Unlike CC, gonadotropin does not exert a peripheral antiestrogenic effect. The main drawback of gonadotropins is that they provoke multiple follicle development, thereby increasing the risk of ovarian hyperstimulation syndrome (OHSS) and multiple pregnancies. Treatment with FSH is expensive, is time consuming, and requires expertise and stringent monitoring. OHSS is related to hCG-mediated production of vasoactive mediators after gonadotropin-induced multifollicular development.

Several treatment protocols have been advocated, such as step-up, low-dose step-up, and step-down regimens. The ASRM recommends low-dose gonadotropin protocols. A step-up dose-finding approach favoring unifollicular development is recommended. The step-up regimen starts with a minimum dose (37.5–50 IU/day), which increases according to the lack of follicle response. Control is made by ultrasound, and the regimen is modified after 1 week of no follicle growth with a 50% increase each time as required. HCG is used as a surrogate for the LH surge, leading to maturation of the oocyte, rupture of the follicle, and formation of the corpus luteum. The step-down regimen starts with the maximum recommended dose, which is reduced as a follicle response is achieved. The dose is reduced by 50% each time the regimen is changed. Recent studies have demonstrated greater safety for patients using the step-up regimen.

In 2006, the ASRM advocated caution and strict control when blood estradiol levels exceed 2500 pg/mL during induction.39 Current recommendations suggest withholding hCG administration in the presence of more than two follicles >16 mm or more than one follicle >16 mm and two additional follicles >14 mm, or if serum estradiol levels are between 1000 and 2500 pg/mL, particularly in women <38 years old without any other infertility factors. Overall, low-dose regimens resulted in a monofollicular ovulation rate of ~70%, a pregnancy rate of 20% per cycle, and a multiple live birth rate of 5.7% while maintaining a low incidence of multiple pregnancies (<6%) and OHSS (<1%). A maximum of six cycles with gonadotropins is recommended because no response with six cycles signifies resistance.

Laparoscopic ovarian diathermy

In clomiphene-resistant PCOS women who are unable to comply with the close monitoring necessary for gonadotropin administration, bilateral laparoscopic ovarian surgery with monopolar electrocautery (multiple controlled perforation of the ovary) or laser is an acceptable alternative; both modalities confer similar results. Laparoscopic ovarian diathermy (LOD) is associated with lower multiple gestation rates than gonadotropins. In a Cochrane Database Systematic Review article, there was no evidence of a difference in live birth rate and miscarriage rate in women with clomiphene-resistant PCOS undergoing LOD versus gonadotropin treatment. It appears to be more effective in patients with high LH, and significant reductions in LH and androgens have been shown following surgery. LOD restores menstrual regularity in 63%–85% of women, and the beneficial effects on reproductive outcomes seem to last for several years in many women. Treatment with metformin is equally efficacious in correcting the clinical, endocrine, and metabolic abnormalities associated with PCOS.

In vitro fertilization techniques

The last possibility for achieving a full-term pregnancy in women with PCOS is to use in vitro fertilization (IVF) techniques. Patients with PCOS are characterized by anovulatory cycles that conceptually are not an indication for IVF techniques. These techniques are used as a last resort when treatments with CC, gonadotropins, and letrozole have failed. IVF is the first choice in cases of concomitant diseases both in women (severe endometriosis, tubal obstruction, etc) and men (azoospermia, male factor) that reduce the effectiveness of other techniques. Because of the increased risk of multiple gestations (up to 10%) with gonadotropin induction in anovulatory women with PCOS, IVF is a reasonable alternative for women seeking pregnancy. IVF with a single embryo transfer significantly reduced the risk of multiple gestation. IVF allows the

placement of only one embryo or for cryopreservation of all embryos, with transfer of a single embryo in a subsequent cycle with endometrial but not ovarian stimulation IVF.

Several stimulation protocols have been published for the treatment of patients with PCOS undergoing IVF, including combinations or isolated use of clomiphene, human menopausal gonadotropins, recombinant FSH, GnRH agonists, and GnRH antagonists. According to the 2008 ASRM consensus conference, the most commonly employed protocol is a long FSH desensitization protocol in which an agonist is started in the early, mid-, or late luteal phase in the preceding cycle or in the follicular phase until hCG administration. Stimulation with gonadotropins is started when pituitary and ovarian suppression has been achieved. A meta-analysis published in 2006, which studied the results of conventional IVF techniques in women with PCOS, revealed more cycle cancellation and that the duration of stimulation cycles was significantly longer in women with PCOS. There is evidence that the use of metformin improves viable pregnancy rates and reduces the incidence of OHSS. The success of IVF techniques is similar to that of patients without PCOS, which implies that PCOS does not intervene in embryo implantation.

Treatment of menstrual dysfunction

Chronic anovulation is associated with an increased risk of endometrial hyperplasia and carcinoma.51 Thus, it is prudent to consider endometrial biopsy in patients with PCOS who have not had menstrual bleeding for a year or longer. Some investigators have advocated the use of ultrasonography to determine endometrial thickness in deciding whether to do a biopsy of the endometrium. Endometrial proliferation can be inhibited by administering either cyclic progestin or oral contraceptives with a combination of estrogen and progestin. The latter approach, which also reduces ovarian androgen production, may be particularly beneficial in this setting.[47]

Unani Treatment:

Physicians of Unani system of medicine described various diseases in this category, such as *Qillat e Tams, Ihtibaz e Tams, Uqr*. The causes, clinical features of above conditions are almost same. The causes of *Uqr* in female due to obesity and PCOS as described by modern medicine are very much similar to the causes and features of *Uqr*. But the cellular and hormonal concept in relation to this disorder is recent. Therefore it is commonly believed that the understanding the approach of management of Unani system of medicine towards Uqr due to obesity and PCOS in female is fundamentally different from the Modern science.

The treatment methodology of the Unani system of medicine is called *Ilaj bil Zid.* It means, the medicine which has the opposite *Mizaj* (Temperament) of the affected akhlat is chosen and the

patient treated with it. In our hospital usually we practiced modified *Ilaj bil Tadabeer* (Regimental therapy- such as *Munzij, Mushilalt, Nutool, Inhibab, Riyasat*) for overcome this problem.

Keeping above principles to correct involved *Ghir e tabayee mada* (Abnormal humours)such as *Ghir e tabayee Balgham vo Sawda,* give following *Unani Joshanda*(Decoction)which have the action of *Munzij e balgham* for *Ghir e Tabayee Balgham* and the *Munzij e Sawda* for *Ghir e Tabayee Sawda* should prescribed in the dose of half a cup morning and the evening for 12 to 14 days .But if the *Ghir e Tabayee Sawda* is *Ghaleez* in *Khiwam* then we should be give the *munzij* in recurrently. In this condition selection of *dawa* should also have the action of *Mudir – e Haiz*(Emmenogogue) and *Muqawwi e A'za e Rayeesa* (General tonic for vital organs)[48]

Munzij e Balgham*:*

Badiyan, Asal e soos, Usthakhudoos, Izkhar, Kibr, Perciaushan, Zeer e Siya.

Munzij e Sawda:

Badaraj boya, Usthakhudoos, Badiyan, Unanb, Thuranjabeen, Shahathira After maturation / coctives of *Ghair e tabayee Mada*, the maturation *mada* has to be expelled by giving *Mushilat* (Purgatives). If the involved *Mada* is *Ghair e Tabayee Balgham* give following *Joshanda* for 3 Days,

Mushil e Balgham:

Sheham e Hanzal, Bisfaij, Thurbud, Sibr, Sena makki, Amalthas. Mean time, involved *Mada* is *Ghir e Tabayee Sawda* gives following *joshanda* for 3 days,

Mushil e Sawda:

Haleel e Siya, Jamal gota, Sheham e Hanzal, Afthimoon, Sena makki. As a local stimulation *Nutool* (Pouring oil / decoction) by *Garam joshanda* of *Qust* or *Panchankhust* or *Roghan e Qust* or *Garam Milk* given to lower abdominal area in the period of *Munzij* for 15 – 30 minutes per a day. Moreover, *Inhibab* also gave in every morning with *Joshand e Panchankust and Barg e Adosa.* After 15 days treatment patients were discharged by reduction of body weight with the feeling of comfortable. Medicines were prescribed to regulate the menstrual cycle (*Mudir e Haiz*), uterine tonic (Muqawwe *Reham*) and strengthen the vital organs (*Muqawwe A'za e Ra'eeza*) for next 7 days. Moreover, some lifestyle modification including diet and physical activities also advised to maintain properly.

Muqawwe Reham:

Majoon e Falasifa

Majoon e Supari Pak

Habb e Hamal

Majoon e Muqawwe Reham

Dawa ul Kurkum

Safoof e Thabashir

Dawa ul Misk

One of the most important factors for maintaining healthy functioning is to have a lifestyle that does not disturb natural bodily rhythms. Therefore, regularity in daily routine work and *Riyasat* (Exercise) *should* also be extremely very effective in reducing physiological imbalance due to life style problem such as PCOS.

- All Physical activities counts
- Walk instead of taking the car / three wheeler / bus: 30 minutes brisk walking will burn 144 calories.
- Switch off the television and go for a walk
- Take the stairs instead of the lift
- Improve the home garden

Even moderately active gardening will expend 50 K. cal more than watching television. A diet for weight loss and weight management is high in fiber and low in fat. The bulk of the diet advised to come from cereals, fruits and vegetable groups and that at least some of the servings are high in non starch fiber. These therapies are not only effective at removing the imbalances at the basis of chronic disorders but also have no significant side effects. The goal of this Unani approach is to enliven the body's natural healing, uplift the *Tabeya't* and self – repair ability not only to help cure anovulatory cycle but also prevent disorders and create the highest state of health and well- being.

A number of single drugs like *Alsi* (Linum usitatissimum), *Zafran* (Crocus sativus), *Zanjbeel* (Zingiber officinalis), *Ood saleb* (Paeonia officinalis), *Musali siyah* (Curculigo orchiodes), *Beejband* (Sida cardifolia), *Aslussoos* (Glyceyrrhiza glabra) etc[49] and compound formulations like *Jawarish moene hamal*, *Habbe moene hamal, Safoof istaqrare hamal, Majoon hamal ambary* etc[50] are widely used in the management of ehtebase tams and uqr. Many scientific studies have proven the effect of Unani drug like *Aelva* (Aloe barbadensis).[51] *Sarphunka* (Tephrosia purpurea),[52] *Lajvanti* (Mimosa pudica)[53] on PCOS. *Asgand* (Withania somnifera Dunal.) and *Kharekhask* (Tribulus terristris Linn.) are important drugs of Unani medicine. Both the drugs are described to possess muwallide mani, mudirre haiz and muqawwi bah activities.[49] Many scientific studies have been carried out on these drugs and reported for *Asgand* to possess

anti-stress, antioxidant, anti-carcinogenic, anti-aging, cardio protective,hypothyroid, immunomodulatory, antifungal, antibacterial, hypocholesterolemic, hypolipidemic and CNS related activities.[54] Kharekhask possess antiurolithiatic, aphrodisiac, CNS stimulatory and cardio tonic activities.[55]

Five common medicines that help in the management of PCOS:

1. ***Satawar* (Asparagus racemosus)**

Satawar helps in promoting normal development of ovarian follicles, regulates menstrual cycle and revitalizes the female reproductive system. *Satawar* also helps in combating the hyperinsulinemia- i.e. high levels of insulin, mainly due to its phytoestrogen (natural plant based estrogen)[56]

2. ***Giloe*(Tinospora Cordifolia)**

Giloe is a powerful anti- inflammatory herb. Chronic inflammation in tissues is the root cause for insulin imbalance and ovarian cysts. *It* helps in revitalizing all the body tissues and boosts metabolism naturally. It also helps in lowering insulin resistance.

3. ***Saunf* (Foeniculum vulgare)**

They are rich source of phytoestrogens. Phytoestrogens in fennel, helps in reducing insulin resistance and in bringing down the inflammation in PCOS. Phytoestrogens are also believed to help reduce the cellular imbalance which leads to metabolic disturbances in PCOS[57]

4. ***Triphala***

A mixture of three fruits- Amla (Emblica officinalis), Halela (Terminalia chebula) and Balela (Terminalia bellerica) blended in it. It is a rich source of vitamin C- a powerful natural antioxidant that helps in reducing inflammation by scavenging free radicals. *Triphala* helps in cleansing and detoxifying .

5. ***Aelva* (Aloe barbadensis)**

It helps in regularizing the menstrual cycles, promotes normal mestruation and normalizes ovarian hormonal imbalance.[58]

REFERENCES

1. Kollmann M, Martins WP, Raine-Fenning N (2014). "Terms and thresholds for the ultrasound evaluation of the ovaries in women with hyperandrogenic anovulation". *Hum. Reprod. Update* 20 (3): 463–4. doi:10.1093/humupd/dmu005. PMID 24516084.

2. "USMLE-Rx". MedIQ Learning, LLC. 2014. "Stein-Leventhal syndrome, also known as polycystic overy syndrome (PCOS), is a disorder characterized by hirsutism, obesity, and amenorrhea because of luteinizing hormone-resistant cystic ovaries."
3. Page 836 (Section:*Polycystic ovary syndrome*) in: Fauser BC, Diedrich K, Bouchard P, Domínguez F, Matzuk M, Franks S, Hamamah S, Simón C, Devroey P, Ezcurra D, Howles CM (2011). "Contemporary genetic technologies and female reproduction". *Human Reproduction Update* 17 (6): 829–847. doi:10.1093/humupd/dmr033. PMC 3191938. PMID 21896560.
4. Legro RS, Strauss JF (September 2002). "Molecular progress in infertility: polycystic ovary syndrome". *Fertility and Sterility* 78 (3): 569–576. doi:10.1016/S0015-0282(02)03275-2. PMID 12215335.
5. Diamanti-Kandarakis E, Kandarakis H, Legro RS (August 2006). "The role of genes and environment in the etiology of PCOS". *Endocrine* 30 (1): 19–26. doi:10.1385/ENDO:30:1:19. PMID 17185788.
6. Marrinan, Greg (20 April 2011). Lin, Eugene C, ed. "Imaging in Polycystic Ovary Disease". *eMedicine*. eMedicine. Retrieved 19 November 2011.
7. Kovacs, Gabor T.; Norman, Robert (2007-02-22). *Polycystic Ovary Syndrome*. Cambridge University Press. p. 4. ISBN 9781139462037. Retrieved 29 March 2013.
8. Richard Scott Lucidi (25 October 2011). "Polycystic Ovarian Syndrome". eMedicine. Retrieved 19 November 2011.
9. Azziz R (March 2006). "Diagnosis of Polycystic Ovarian Syndrome: The Rotterdam Criteria Are Premature". *Journal of Clinical Endocrinology & Metabolism* 91 (3): 781–785. doi:10.1210/jc.2005-2153. PMID 16418211.
10. The Rotterdam ESHRE/ASRM-sponsored PCOS consensus workshop group (2004). "Revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome (PCOS)". *Human Reproduction* 19 (1): 41–47. doi:10.1093/humrep/deh098. PMID 14688154. Retrieved 14 November 2011.
11. Goldenberg N, Glueck C (2008). "Medical therapy in women with polycystic ovary syndrome before and during pregnancy and lactation". *Minerva Ginecol* 60 (1): 63–75. PMID 18277353.
12. Boomsma CM, Fauser BC, Macklon NS (2008). "Pregnancy complications in women with polycystic ovary syndrome". *Semin. Reprod. Med.* 26 (1): 72–84. doi:10.1055/s-2007-992927. PMID 18181085.

13. Azziz R, Woods KS, Reyna R, Key TJ, Knochenhauer ES, Yildiz BO (June 2004). "The Prevalence and Features of the Polycystic Ovary Syndrome in an Unselected Population". *Journal of Clinical Endocrinology & Metabolism* 89 (6): 2745–9. doi:10.1210/jc.2003-032046. PMID 15181052.
14. Teede H, Deeks A, Moran L (2010). "Polycystic ovary syndrome: a complex condition with psychological, reproductive and metabolic manifestations that impacts on health across the lifespan". *BMC Med* 8: 41. doi:10.1186/1741-7015-8-41. PMC 2909929. PMID 20591140.
15. D.C.Dutta.Text Book of Gynaecology.5th ed.New Delhi:New Central Book Agency(P) LTD;2008:440
16. Mayo Clinic Staff (4 April 2011). "Polycystic Ovary Syndrome – All". *MayoClinic.com*. Mayo Clinic. Retrieved 15 November 2011.
17. Christine Cortet-Rudelli, Didier Dewailly (Sep 21, 2006). "Diagnosis of Hyperandrogenism in Female Adolescents". *Hyperandrogenism in Adolescent Girls*. Armenian Health Network, Health.am. Retrieved 2006-11-21.
18. Huang A, Brennan K, Azziz R (April 2010). "Prevalence of hyperandrogenemia in the polycystic ovary syndrome diagnosed by the National Institutes of Health 1990 criteria". *Fertil. Steril.* 93 (6): 1938–41. doi:10.1016/j.fertnstert.2008.12.138. PMC 2859983. PMID 19249030.
19. Nafiye Y, Sevtap K, Muammer D, Emre O, Senol K, Leyla M (April 2010). "The effect of serum and intrafollicular insulin resistance parameters and homocysteine levels of nonobese, nonhyperandrogenemic polycystic ovary syndrome patients on in vitro fertilization outcome". *Fertil. Steril.* 93 (6): 1864–9. doi:10.1016/j.fertnstert.2008.12.024. PMID 19171332.
20. Vos T, Flaxman AD, Naghavi M, Lozano R, Michaud C, Ezzati M, Shibuya K, Salomon JA, Abdalla S, Aboyans V, et al. (Dec 15, 2012). "Years lived with disability (YLDs) for 1160 sequelae of 289 diseases and injuries 1990-2010: a systematic analysis for the Global Burden of Disease Study 2010". *Lancet* 380 (9859): 2163–96. doi:10.1016/S0140-6736(12)61729-2. PMID 23245607.
21. Strauss JF (November 2003). "Some new thoughts on the pathophysiology and genetics of polycystic ovary syndrome". *Annals of the New York Academy of Sciences* 997: 42–48. doi:10.1196/annals.1290.005. PMID 14644808.
22. Kumar Cotran Robbins: Basic Pathology 6th ed. / Saunders 1996

23. Fukuoka M, Yasuda K, Fujiwara H, Kanzaki H, Mori T (1992). "Interactions between interferon gamma, tumour necrosis factor alpha, and interleukin-1 in modulating progesterone and oestradiol production by human luteinized granulosa cells in culture". *Hum Reprod* 7 (10): 1361–4. PMID 1291559.
24. Murri M, Luque-Ramírez M, Insenser M, Ojeda-Ojeda M, Escobar-Morreale HF (2013). "Circulating markers of oxidative stress and polycystic ovary syndrome (PCOS): a systematic review and meta-analysis". *Hum. Reprod. Update* 19 (3): 268–288. doi:10.1093/humupd/dms059. PMID 23303572.
25. Kelly CJ, Stenton SR, Lashen H (2010). "Insulin-like growth factor binding protein-1 in PCOS: a systematic review and meta-analysis". *Human Reproduction Update* 17 (1): 4–16. doi:10.1093/humupd/dmq027. PMID 20634211.
26. Gleicher N, Weghofer A, Lee IH, Barad DH (2010). Mailund, Thomas, ed. "FMR1 Genotype with Autoimmunity-Associated Polycystic Ovary-Like Phenotype and Decreased Pregnancy Chance". *PLoS ONE* 5 (12): e15303.
27. Pedersen SD, Brar S, Faris P, Corenblum B (2007). "Polycystic ovary syndrome: validated questionnaire for use in diagnosis". *Canadian Family Physician* 53 (6): 1042–7, 1041. PMC 1949220. PMID 17872783. – see Table 5 Clinical tool for diagnosis of polycystic ovary syndrome
28. Dewailly D, Lujan ME, Carmina E, Cedars MI, Laven J, Norman RJ, Escobar-Morreale HF (2014). "Definition and significance of polycystic ovarian morphology: a task force report from the Androgen Excess and Polycystic Ovary Syndrome Society". *Hum. Reprod. Update* 20 (3): 334–52. doi:10.1093/humupd/dmt061. PMID 24345633.
29. O'Brien, William T. (1 January 2011). *Top 3 Differentials in Radiology*. Thieme. p. 369. ISBN 9781604062281. Retrieved 30 August 2014. "Ultrasound findings in PCOS include enlarged ovaries with peripheral follicles in a "string of pearls" configuration."
30. Somani N, Harrison S, Bergfeld WF (2008). "The clinical evaluation of hirsutism". *Dermatologic therapy* 21 (5): 376–91. doi:10.1111/j.1529-8019.2008.00219.x. PMID 18844715.
31. "Polycystic Ovarian Syndrome Workup". eMedicine. 25 October 2011. Retrieved 19 November 2011.
32. Robinson S, Rodin DA, Deacon A, Wheeler MJ, Clayton RN (March 1992). "Which hormone tests for the diagnosis of polycystic ovary syndrome?". *Br J Obstet Gynaecol* 99 (3): 232–8. doi:10.1111/j.1471-0528.1992.tb14505.x. PMID 1296589.

33. Li X, Lin JF (December 2005). "[Clinical features, hormonal profile, and metabolic abnormalities of obese women with obese polycystic ovary syndrome]". *Zhonghua Yi Xue Za Zhi* (in Chinese) 85 (46): 3266–71. PMID 16409817.
34. Banaszewska B, Spaczyński RZ, Pelesz M, Pawelczyk L (2003). "Incidence of elevated LH/FSH ratio in polycystic ovary syndrome women with normo- and hyperinsulinemia". *Rocz. Akad. Med. Bialymst.* 48: 131–4. PMID 14737959.
35. Dewailly D, Andersen CY, Balen A, Broekmans F, Dilaver N, Fanchin R, Griesinger G, Kelsey TW, La Marca A, Lambalk C, Mason H, Nelson SM, Visser JA, Wallace WH, Anderson RA (2014). "The physiology and clinical utility of anti-Mullerian hormone in women". *Hum. Reprod. Update* 20 (3): 370–85. doi:10.1093/humupd/dmt062. PMID 24430863.
36. Broer, S. L.; Broekmans, F. J. M.; Laven, J. S. E.; Fauser, B. C. J. M. (2014). "Anti-Mullerian hormone: ovarian reserve testing and its potential clinical implications". *Human Reproduction Update* 20 (5): 688–701. doi:10.1093/humupd/dmu020. ISSN 1355-4786.
37. Legro RS, Kunselman AR, Dodson WC, Dunaif A (1999). "Prevalence and predictors of risk for type 2 diabetes mellitus and impaired glucose tolerance in polycystic ovary syndrome: a prospective, controlled study in 254 affected women". *J. Clin. Endocrinol. Metab.* 84 (1): 165–9. doi:10.1210/jc.84.1.165. PMID 9920077.
38. World Health Organization. (1992) *WHO laboratory manual for the examination ofhuman semen and sperm- cervical mucus interaction.* 3rd edition. Cambridge: Cambridge University press:52.
39. Dahlgren. E, FribergL.G, Johansson S, Lindstrom B, Oden A, Samsioe G, *et al.*(1991)Endometrial carcinoma; ovarian dysfunction – A risk factor in young women. *Eur J.Obstet Gynecol Reprod Biol*. 41:143-50 . (Pub Med)
40. Ibn Sina. *Al-Qanoon.* (Urdu Translation by Kantori G.H). Vol.3 and 4, New Delhi: Idara Kitabus Shifa; 2010: 1065-1066,1445.
41. Razi AMZ. *Al Kitabul Havi*. Vol. 9, New Delhi: CCRUM; 2001: 151-155.
42. IbnSina. Al QanoonFilTib (Urdu translation by Kantoori GH).New Delhi: IdaraKitab-us-shifa; 2010: 280, 328, 1088-89, 1095-98.
43. Razi ABZ. Al HawiFilTib. Vol IX. New Delhi: CCRUM; 2001:151-68.
44. Qumri AMH. GhinaMuna. 1sted. New Delhi:CCRUM; 2008:410-413, 435-437.

45. Jurjani I. ZakheeraeKhawarzamShahi (Urdu trans. by Khan AH). Vol VI. New Delhi: IdaraKitab-us-shifa; 2010 January: 597-602.
46. Parray SA, Bhat J, Iqbal SMF, Ahmad G, Jahan N, Rahman M. Concept of Obesity (Samane Mufrat) and its consequences in Greeko-Arab Medicine:A Review. Internationale Pharmaceutica Sciencia. 2012; 2(1):1-8.
47. Ahmed Badawy, Abubaker Elnashar. Treatment options for polycystic ovary syndrome. Int J Womens Health. 2011; 3: 25–35.
48. Ar Razi Abu Bakar Mohamed Bin Zakariya, (1961). *Kitabul Hawi Fil Tib* , (Arabic) 1st edition .Vol-10 , Osmaniya oriental Publication Bureau. P-303
49. Gani N. *Khazaienul Advia*. New Delhi: Idara Kitabus Shifa; YNM: 258, 761, 869, 955, 1271, 367, 1260, 230-231, 1156-1158.
50. Khan A. *Qarabadeen-e-Azam*. New Delhi: Aijaz Publishing House; 1996: 39, 88, 424, 578.
51. Maharjan R, Nagar PS, and Nampoothiri L. Effect of *Aloe barbadensis Mill*. formulation on letrozole induced polycystic ovarian syndrome rat model. *J ayurveda Integr Med* Oct-Dec 2010; 1(4): 273–279.
52. Jitendra PA and Pravin TA. Prospective use of *Tephrosia purpurea* in remedial treatment of PCOS: Study in Wistar rat. *ISCA Journal of Biological Sciences* July 2012; 1(3):1-6.
53. Jadhav M, Menon S and Shailajan S. In vivo evaluation of *Mimosa pudica linn.* in the management of polycystic ovary using rat model. *International Journal of Applied Biology and Pharmaceutical Technology* Jan-Mar 2013; 4(1):285-292.
54. Jain R, Kachhwaha S and Kothari SL. Phytochemistry, pharmacology, and biotechnology of *Withania somnifera* and *Withania coagulans*: A review. *Journal of Medicinal Plants Research* 25 Oct 2012; 6(41): 5388-5399.
55. M Jamil, Akhtar AJ, Abuzar A, Javed A, Ali M, Ennus. *Pharmacological scientific evidence for the promise of Tribulus terrestris IRJP* 2012; 3(5): 403-406.
56. Hannan, J. M. A., et al. "Antihyperglycaemic activity of Asparagus racemosus roots is partly mediated by inhibition of carbohydrate digestion and absorption, and enhancement of cellular insulin action." British Journal of Nutrition 107.09 (2012): 1316-1323.
57. Jungbauer, Alois, and Svjetlana Medjakovic. "Phytoestrogens and the metabolic syndrome." The Journal of steroid biochemistry and molecular biology 139 (2014): 277-289.

58. Maharjan, Radha, Padamnabhi S. Nagar, and Laxmipriya Nampoothiri. "Effect of Aloe barbadensis Mill. formulation on Letrozole induced polycystic ovarian syndrome rat model." Journal of Ayurveda and integrative medicine 1.4 (2010): 273.