



A Review of the Gut-Uterine Axis in Persian Medicine Literature: Implications in Polycystic Ovary Syndrome

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Abstract

Persian medicine (PM) takes a holistic approach towards diagnosis and management of disease states, focusing on the connections between body systems and organs. Menstrual disorders are of utmost importance in women, as they may lead to dysfunctions in other body systems. Deeming a mutual relationship between the gastrointestinal and female reproductive systems, PM physicians believed in a *gut-uterine* axis to exist. *Ehtebas-e Tams* (ET), meaning menstrual retention, is not an exception, being accompanied by gastrointestinal morbidities including digestive disorders, nausea, heartburn, food craving and pica, reduced appetite, abdominal pain, and bloody diarrhea. Considering polycystic ovary syndrome (PCOS) as an instance of ET, we searched studies to investigate these correlations. While a number of the mentioned ET symptoms were confirmed by contemporary studies, others had not been investigated widely and are yet to be elucidated. Conducting studies to clarify such correlations has implications in improved diagnosis and novel modes of treatment.

Keywords: Persian medicine; Iranian traditional medicine; Menstrual disorders; Gut-uterine axis; Functional dyspepsia; Eating disorders

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Introduction

Normal menstruation is a marker of women's health [1], and regarded as the fifth vital sign in women by the American College of Obstetricians and Gynecologists [2]. Over a thousand years ago, Avicenna, the renowned Persian physician, observed menstruation as an important factor in women's health status. Considering this monthly cycle as an important factor in maintaining health, he believed that normal menstruation in terms of quantity, quality (color, density, viscosity, etc.) and timing eliminated many harmful substances from a woman's body [3]. Persian medicine (PM) – in some references known as Iranian traditional medicine, practiced for thousands of years, is a humoral medicine based on the belief that the body is a constitution of four humors - blood, phlegm, yellow bile and black bile. Despite its seemingly simplistic nature at first glance, omics-based research has found evidence in support of this categorization [4]. Persian medicine offers a holistic approach toward the body and aims to diagnose and eradicate the roots of a disease with regard to the connections between body organs and systems. PM references consider the uterus, by which they mean the female reproductive system, a cardinal organ, since diseases related to this organ and its function are said to be disseminated in the body to affect all other body systems [5]. In addition to the position they considered for the uterus in relation to other organs, they have also emphasized the close connection between the uterus and gut, or gut-uterus connection. [6] According to PM, a strong correlation exists between the uterus and the gastrointestinal (GI) system. Menstrual disorders including both increased [7,8] and decreased [3,9] menstrual bleeding lead to gastrointestinal (GI) disorders. Conversely, gastrointestinal disorders can initiate diseases in the uterus. Uterus is a general term used by PM scholars to imply the female reproductive system not just the uterus itself [10].

An important gynecologic disorder in Persian medicine is "*Ehtebas-e Tams*" (ET) meaning menstrual retention, whether it be complete cessation of menstruation, an increase in the interval between cycles, or reduction in the amount of bleeding [10]. In modern semiology, this disorder can be regarded as an equivalent to polycystic ovarian syndrome (PCOS) [11,12,13]. According to physicians of Persia, ET is a critical disease with various morbidities that should not by any means be left untreated, as the wastes that should have been excreted via menstruation spread throughout the body, leading to many comorbidities [5]. Avicenna in his book, Canon, under the topic of ET, describes its morbidities. In addition to expressing symptoms such as hirsutism and hoarseness, which are now known as hyperandrogenic symptoms, he referred to the various morbidities of ET in various organs [3], that is shown in Figure 1.

The most prevalent menstrual disorder accompanied by amenorrhea/oligomenorrhea in contemporary literature is polycystic ovarian syndrome (PCOS). It is estimated to affect 10% of women in child-bearing age [14]. Typically developing in adolescence, PCOS continues throughout the reproductive years and is even reported to leave sequela after menopause [15,16]. Many endocrine and metabolic complications including insulin resistance and type 2 diabetes [17,18], dyslipidemia [19], and cardiovascular diseases [20,21] accompany PCOS.

Gastrointestinal (GI) dysfunctions are also present in PCOS, proved by many studies of the recent years that have investigated this correlation. However, many aspects have remained elusive, necessitating yet more studies. The purpose of this study was to review the gastrointestinal morbidities of ET mentioned in PM references, and to investigate whether the symptoms can be applied to PCOS as a disorder accompanied by amenorrhea/oligomenorrhea.

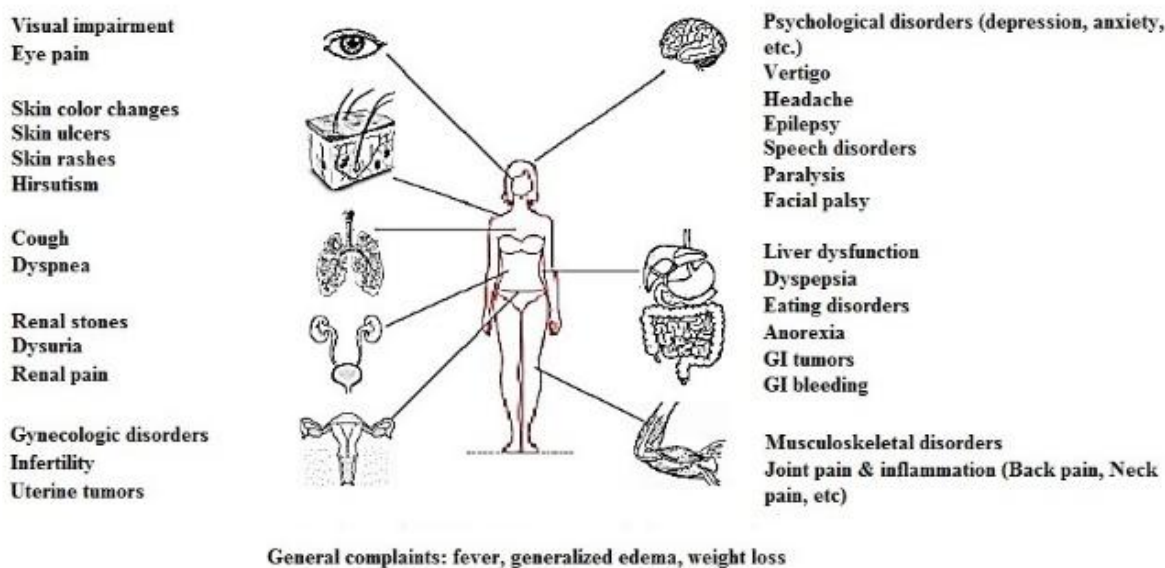


Figure 1: Complications of PCOD from viewpoint of Persian Medicine

Methods

This article is a qualitative study in two branches of traditional Persian medicine and modern literature. We first searched PM references, including Rhazes' "Al-Kitab al Hawi" (10th century), Ahwazi's "Kamil al-Sana'a" (10th century), Avicenna's "Canon of Medicine" (11th century), Akbari's Tebb-e-Akbari (18th century), Nazem Jahan's encyclopedia of "Exir-e Azam" (19th century) for words related to "Ehtebas-e tams" and gathered the data on the associated gastrointestinal morbidities. The data were then classified, coded, and analyzed. In the next step, we searched PubMed and Scopus databases using the words polycystic ovary syndrome, and each of the gastrointestinal symptoms found in PM references in combination.

Results and Discussion

Gastrointestinal morbidities of ET in PM literature include indigestion, heartburn, nausea, GI inflammation, anorexia, food craving and pica, excessive thirst, GI bleeding, intraabdominal tumors [5,10]. In the following, each morbidity will be outlined as discussed in PM references and then investigated for any rela-

tion with PCOS in contemporary literature.

Indigestion

ET can be accompanied by digestion weakness and deterioration. Digestion disorders as described by PM scholars include a spectrum of conditions, the mildest of which is named "digestion weakness", defined as the inability of the digestive faculty to transform food into a desirable quality to be optimally used by the body [22]. This disease is diagnosed by symptoms of delayed gastric emptying [23], postprandial fullness, abdominal distention, abdominal bloating and belching [5].

"Digestion deterioration", is a more severe form of digestion dysfunction, accompanied by symptoms of liver dysfunction in addition to gastrointestinal symptoms [3]. Both of these conditions and also heartburn and nausea have been mentioned to occur in ET [3], depending on the severity and duration of disease. [3,7,9]. Symptoms of *digestion weakness* described by PM scholars resemble functional dyspepsia in contemporary medicine. Functional dyspepsia (FD), typically chronic and recurrent in nature [24], refers to cases where no evidence of struc-

tural disease likely to explain the symptoms can be found [24,25]. The prevalence of FD is estimated to be 5-15% in the general population, excluding cases of heartburn [27]. Affected individuals complain of upper abdominal fullness, nausea, early satiety, belching and bloating [28]. However, to increase specificity to the gastroduodenal area, Rome IV confined the main symptoms to early satiety, postprandial fullness, epigastric pain and epigastric burning [29].

Since many cases are meal related and aggravated following food ingestion, FD is categorized into three subtypes: 1) postprandial distress syndrome (PDS): characterized by post prandial fullness and early satiation, 2) epigastric pain syndrome (EPS): characterized by pain and burning in the epigastric region, and 3) overlapping subtype: characterized by overlapping features of PDS and EPS [29].

Gastric dysmotility or hypersensitivity is observed in two thirds of FD patients [30]. Four main factors were defined in a cluster analysis of dyspeptic symptoms in several hundred patients: 1) nausea, vomiting, weight loss and early satiety associated with female sex and young age; 2) postprandial fullness and bloating; 3) pain associated with psychosocial factors; and 4) belching unrelated to psychosocial factors. The first two factors were associated with delayed gastric emptying while the two latter were associated with gastric hypersensitivity [31].

Our search revealed no direct relationship between dyspepsia, gastrointestinal motility, or hypersensitivity and PCOS. However, a number of mechanisms have been hypothesized to play a role in FD, which were investigated in terms of relations with PCOS.

Some recent studies have explored the relationship between PCO and GI diseases, one of the most important of which is research on the gut microbiome, the collective microorganisms that are resident in the GI tract. Microbiome al-

terations have been found in rodent PCO models [32,33]. This is also true in humans, as the fecal microbiome in PCO affected individuals has less diversity and a different phylogenetic profile compared to healthy controls [34]. Microbiome shift results in an augmented gut permeability [35], which in turn induces endotoxemia and inflammation, a process that has been proposed to play a role in the pathogenesis of PCO [36]. Additional evidence in favor of increased gut permeability in PCO individuals is a report of an increase in serum zonulin, the only known biomarker of gut permeability [35].

Other proposed mechanism for FD is infection with *Helicobacter Pylori* and the resultant gastric and duodenal mucosal inflammation [37]. A possible relationship between *H. Pylori* infection and PCOS has been propounded in the recent years. Some studies have confirmed a more prevalent positive serology in PCOS patients [38], while others have not found this correlation to be true [39,40].

Central nervous system mechanisms have also been implicated in the pathogenesis of functional dyspepsia, including cerebral glycometabolic disturbances have been found in certain brain regions [41]. There are also evidences of abnormal brain activity in FD patients aggravated by anxiety [42]. In a population based study, a correlation between anxiety with the PDS, but not the EPS subtype was found, which supports the idea of different pathophysiologies of the subgroups [43]. This mechanism may be applicable to PCOS, as anxiety has been found to be more prevalent in this population [44]. Regarding it, PM scholars declare one of the morbidities of ET to be anxiety [8,45].

Eating Disorders

Food craving and Pica

Pica was first described by Hippocrates, who viewed it as a yearning in pregnant women to consume earth or charcoal [46]. The desire

to ingest inappropriate foodstuff, so-called “*vahm*” or “*fasad-e shahvat*” in PM [47], is categorized into two subtypes. One is associated with a pathologic desire towards a specific taste such as salty, sour, or hot food, while the other is a yearning for non-nutritional substances like earth, ice, or charcoal [47,48]. According to Canon of Medicine, the first subtype is seen in mild diseases, whereas more severe pathologies are associated with the second subtype [3]. *Vahm* is more common in women and children, due to the higher percentage of moistures in their bodies [49]. Etiologies in women, as described by PM literature include ET and early pregnancy [3,10,47]. Since *Vahm* includes desire towards both certain foods and non-nutritional substances, it can be regarded as an equivalent to respectively, food craving and pica.

Food craving (FC), is more common in women, of whom a third report correlations with the menstrual cycle [50]. Overall, 58% of women experience FC, with 7% occurring only during pregnancy. Narrowing the definition to moderate and severe craving reduces the incidence to 42% and 21% respectively [51]. Considering the higher perimenstrual and prenatal prevalence of FC, hormonal mechanisms have been proposed [52].

Evidences regarding PCOS correlations with food craving are found in modern literature. In a recent cohort of obese and overweight PCOS patients, FC was demonstrated to be more prevalent compared to healthy women [53]. Likewise, in the largest study investigating the relationship between PCOS and eating disorders, it was reported that food craving was significantly more prevalent in obese PCOS patients compared to lean and overweight affected individuals [54].

PCOS is also associated with eating disorders, namely binge eating disorder (BED) and bulimia nervosa. DSM-5 defines bulimia nervosa as recurrent episodes of binge eating, i.e. con-

sumption of larger amounts of food in a discrete period than is typical for most people and a lack of control of eating during these episodes along with recurrent inappropriate compensatory behavior such as self-induced vomiting or laxative abuse for a duration of at least once a week for three weeks, while in BED there is no compensatory behavior [55].

In a large population-based study, women who reported lifetime binge eating were more likely to report either amenorrhea or oligomenorrhea than women who had not experienced binge eating [56]. Specifically speaking of PCOS, a number of studies have reported no correlations with eating disorders [57,58], while other research in this regard indicate higher prevalence of eating disorders in these patients [59-61]. Results of the largest study in this regard, indicate that over half of obese PCOS patients experience binge eating behavior, about 40% of which are clinically significant. Moreover, binge eating is more prevalent in lean women with PCOS compared to healthy controls [54]. Binge eating disorder resemble “*Joo-e kalbee*”, a subtype of “*fasad-e shahvat*” which defined by uncontrolled desire for eating food. PM scholars declare one of the morbidities of ET to be “*fasad-e shahvat*”.

Anorexia

PM references categorize appetite as true and false. True appetite is the desire to consume food consequent to the body’s need for food, while false appetite refers to pathologic states that are a result of dysregulation in production and secretion of appetite regulating factors, and lead to abnormal eating patterns [3,8]. A true appetite is the result of depletion in body stores and need a healthy stomach to detect appetite stimulants [5,10]. Since ET is associated with incomplete expulsion of body wastes and gastrointestinal dysfunction [48], PM practitioners have proclaimed that this menstrual disorder

may result in suppression, and in prolonged cases, complete loss of appetite [3,10].

Studies regarding appetite and satiety in PCOS have yielded conflicting results. Some show no difference in satiety index levels during meal tolerance test or standard meal consumption compared to controls [62,63], while others indicate dysregulations in this respect. Exploring hormones that control hunger and satiety, including leptin, ghrelin, cholecystokinin, glucagon-like peptide-1 (GLP-1), peptide tyrosine-tyrosine (PYY), neuropeptide Y (NPY) will help create a clearer picture of appetite regulation in PCOS. Leptin, an adipocyte-derived hormone, suppresses appetite, stimulates thermogenesis, and reduces body fat mass [64]. A number of studies have demonstrated that leptin is increased in PCOS independent of insulin resistance and that this effect may have a role in the pathogenesis of this disease [65-68]. The peptide hormone, GLP-1, acts as a modulator of insulin secretion, glucose homeostasis, satiety and gastric emptying [69]. A number of studies have investigated fasting and stimulatory levels of GLP-1 in PCOS, most of which have reported levels of it to be unaltered in both states [70], although there are instances of both decreased [71] and increased [72] concentrations of fasting and stimulatory GLP-1.

As a product of intestinal cells, Cholecystokinin (CCK), has a role in induction of satiety, delaying gastric emptying, pancreatic beta cells proliferation, and glucose lowering effects [73]. In a clinical study, PCOS patients have been demonstrated to have low postprandial CCK [74]. Neuropeptide Y (NPY), a member of the NPY family of biologically active peptides, regulates appetite and is increased in both obese and non-obese cases of PCOS, independent of the increase in BMI [75]. PYY, mainly secreted from L-cells of distal intestine in response to food intake, suppresses appetite [76]. Levels of this peptide were found to be unaltered in four

of the five studies that have investigated its concentrations in PCOS patients [70]. One clinical trial reported lower basal and postprandial total PYY levels in PCOS, which correlated negatively with insulin levels [77].

Therefore, it seems that appetite regulation may be impaired in women with PCOS, but to our knowledge no study has investigated the prevalence or associations of Anorexia in PCOS.

GI Bleeding

Al-Zahrawi, in his thirty-volume encyclopedia of medical practices, *Kitab al-Tasrif*, which has been a reference for Islamic and European medicine for more than five centuries, has mentioned ET as a differential diagnosis of bloody diarrhea. He believes the treatment of this disorder to be correcting the menstrual problem and boosting liver function [78].

The most common causes of lower gastrointestinal bleeding in adults include hemorrhoids, diverticula, vascular ectasias, neoplasms, and colitis—most commonly infectious or idiopathic inflammatory bowel disease. In adolescents, the most common colonic causes of significant GIB are inflammatory bowel disease and juvenile polyps [21]. To our knowledge, there is no investigation on the prevalence of the above mentioned causes of lower gastrointestinal bleeding in women with PCOS.

Intraabdominal Tumors

Avicenna, in his book, *Canon*, has mentioned ET as a risk factor for progression of intraabdominal tumors [3]. A cohort study in 2015 revealed that PCOS patients are at increased risk of colon and kidney cancers [81]. This association may be due to different conditions that accompany PCOS, including sex hormones and androgens effect on incidence of GI cancers [82,83] or adipose tissue role in development of cancers [84] or association of decreased insulin sensitivity

and cancer progression [85] and finally the role of obesity in development of gastrointestinal tumors [86]. By the way more studies are needed to clarify association of intraabdominal cancers and PCOS.

Conclusion

This study attempted to review the gastrointestinal morbidities of ET (menstrual retention) mentioned in Persian medicine references, and to investigate whether the symptoms correlate to PCOS, based on evidences from contemporary literature. According to PM, a strong connection exists between the uterus and the gastrointestinal (GI) system, which is of great importance in diagnosis and treatment of disorders in both systems. Menstrual disorders lead to gastrointestinal (GI) disorders, and conversely, gastrointestinal disorders can initiate diseases in the uterus, the female reproductive system. Specifically, menstrual disorders are considered in the differential diagnosis of gastrointestinal disease, and are therefore a target in the treatment process. Also, due to the mutual nature of this correlation, improving gastrointestinal functions is a necessary component of treating menstrual disorders.

Therefore, there may be a relation between gastrointestinal disorders like functional dyspepsia and PCOS, that according to PM may be resolved by treating the main disease. Ideas proposed for future research would be to investigate this correlation and to see whether reconstituting normal menses leads to a decrease in gastrointestinal disorders such as FD cases as proposed by Persian physicians.

Despite evidences in favor of such a correlation in contemporary studies, there are still many ambiguous and in some instances conflicting results necessitating further studies to elucidate these associations. We believe that the all-inclusive detailed data of modern medicine, integrated with the holistic vision of traditional Persian

medicine can yield a more comprehensive view toward the human body in terms of health maintenance, diagnosis, and management of any disease.

Declaration of interest

The authors declare that there is no conflict of interest

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