



## Views &amp; Comments

## Applying TCM Constitution Theory to Infertility via Omics

Qi Wang

National Institute of TCM Constitution and Preventive Medicine, Beijing University of Chinese Medicine, Beijing 100029, China



Polycystic ovary syndrome (PCOS) has become a major international public health concern, affecting 5%–10% of women of reproductive age around the world [1]. The prevalence of PCOS in China has increased significantly over the past ten years [2], which is partially attributed to rapid changes in lifestyle, including diet [3]. Lifestyle modification has led to widespread obesity in China, which is thought to be responsible for the increasing prevalence of PCOS, especially in rural women at least [4]. Women with PCOS commonly manifest through menstrual abnormalities, hirsutism, obesity, and two or more other symptoms, and infertility occurs in up to 80% of cases [5]. PCOS also contributes to other long-term health risks, especially that of type II diabetes mellitus (DM2) [6]. Genetics play an important role in the pathogenesis of PCOS. To date, more than 200 candidate genes have been identified, involving sex hormones, insulin action, calcium signaling, and so forth. PCOS is considered to be a complex multigenic disorder with strong environmental influences, such as diet and lifestyle factors [1]. According to the Rotterdam criteria, which are widely applied diagnostic criteria for PCOS, the features of PCOS are clinical and/or biochemical hyperandrogenism (HA), ovulatory dysfunction (OD), and polycystic ovarian morphology (PCOM). Therefore, the PCOS phenotypes are classified as phenotype-A (HA + OD + PCOM), phenotype-B (HA + OD), phenotype-C (HA + PCOM), and phenotype-D (OD + PCOM) [7]. Similarly, four traditional Chinese medicine (TCM) syndromes are associated with infertility in women according to TCM theory, including liver depression syndrome, blood stasis syndrome, phlegm dampness syndrome, and phlegm-blood stasis syndrome.

A new branch of TCM known as TCM constitution considers that a specific TCM constitution is determined by inborn and acquired factors and can be regulated via acquired factors such as diet, lifestyle, and the surrounding environment [8]. Nine TCM constitutions have been proposed [8]. There are significant differences in multiple dominants among these constitutions, including single-nucleotide acid polymorphism (SNP), metabolic profiles, and gut microbiota [9]. For example, the “phlegm-dampness” constitution has been shown to be associated with upregulated genes, including *COPS8*, *GNPDA1*, *CD52*, and *ARPC3*, as well as a higher body mass index (BMI), higher triglyceride (TG) levels, and higher total cholesterol levels [10]. Interestingly, the clinical and biochemical traits of phenotype-A and -C in PCOS partially overlap with those of the “phlegm-dampness” and “blood-stasis” constitutions, respectively [11]. Thus, it has been considered whether improving and/or reversing the “phlegm-dampness” constitution by means of

diet or TCM formulas, for example, could provide a clinical benefit for PCOS and its associated infertility. Negative relationships between general and central obesity and a traditional diet (i.e., high intake of rice, pork, and vegetables) among older Chinese people have been preliminarily reported, as well as the inverse for a modern diet (i.e., high intake of fruit, fast food, and processed meat) [12]. Moreover, some TCM formulas, such as the “phlegm-dampness constitution conditioning formula,” can significantly lower BMI, TG, low-density lipoprotein (LDL), and the phlegm-dampness score [13]. Therefore, it is plausible that modulating the constitution of an individual could provide a new approach to managing and preventing PCOS and even infertility, based on the principle that a certain constitution predisposes individuals to specific disease susceptibilities [8]. Nevertheless, the issue of how to quantify and standardize TCM constitution classification presents a major challenge.

Recently, a study by Wu et al. [14] investigated the impact of genomic variations and metabolic signatures on fertility outcomes in infertile patients with PCOS. In this study, genomic and metabolomic analyses were performed on serum samples derived from a randomized control trial (PCOSAct) [15]. Whole-exome sequencing and targeted SNP sequencing with ultra-performance liquid chromatography (UPLC) were employed to identify genome-wide variants and metabolite signatures, respectively. The main strength of the study was that it integrated clinical data, genomic and metabolic traits, and TCM syndromes (including kidney deficiency and liver depression, kidney deficiency and blood stasis, spleen deficiency and phlegm dampness, and phlegm-blood stasis) into a complete analysis by means of machine learning, in order to fully understand the mechanism of ovarian response failure to pharmacological treatment. The researchers found that a common variant *ZNF438* and a rare variant *REC114* were significantly associated with failure to respond to ovulation induction in infertile patients with PCOS, along with the two identified metabolic signatures of phenylalanine and arachidonic acid. *L*-phenylalanine was also positively associated with homeostatic model assessment for insulin resistance (HOMA-IR) and fasting glucose, while prostaglandins and hydroperoxides were negatively associated with total testosterone (TT) and anti-Müllerin hormone (AMH), respectively. In addition, the metabolic signature, biochemical index, and clinical features linked with the *ZNF438* and *REC114* variants align with the “phlegm-dampness” and “blood-stasis” constitutions, respectively. This study shows how to link the inborn and acquired factors in a

TCM constitution with genomic and metabolic features in modern biology to elucidate the scientific nature of TCM constitution theory using omics. Nevertheless, one study is far from enough to establish a holistic recognition system for the use of TCM constitution theory to treat and/or prevent PCOS and even infertility, due to a lack of knowledge of the genomic, proteomic, and metabolomic traits associated with specific constitutions. Further studies are needed.

In conclusion, PCOS has become the most important cause of infertility in reproductive-age females and is often the motivation for seeking medical care in this population. Although first-line pharmacotherapy, such as clomiphene, is effective, up to 40% of women with PCOS fail to ovulate. Because patients with PCOS frequently suffer from an abnormal BMI, lifestyle modification targeting weight management is also recommended as a fundamental treatment for this disease. This treatment aligns with the conception of the TCM constitution, which reflects the individual's present status and future tendencies, providing an approach to manage and/or prevent PCOS and even infertility. TCM constitution regulation can affect PCOS on multiple levels, such as by stimulating folliculogenesis, alleviating hyperandrogenism, and improving insulin resistance; it is also well tolerated. While the underlying mechanisms of these benefits have not been fully elucidated and the safety of such treatment is largely unknown, both are expected to be clarified by means of modern biological approaches, such as omics, and clinical evidence. Moreover, due to individual regimens, TCM treatment is difficult to reproduce, which limits its generalization—an issue that may be solved by standardizing TCM patterns and constitution scores. Regardless, TCM constitution regulation may serve as an alternative option to aid first-line treatment.

## References

- [1] Escobar-Morreale HF. Polycystic ovary syndrome: definition, aetiology, diagnosis and treatment. *Nat Rev Endocrinol* 2018;14(5):270–84.
- [2] Li R, Zhang Q, Yang D, Li S, Lu S, Wu X, et al. Prevalence of polycystic ovary syndrome in women in China: a large community-based study. *Hum Reprod* 2013;28(9):2562–9.
- [3] Yang R, Li Q, Zhou Z, Qian W, Zhang J, Wu Z, et al. Changes in the prevalence of polycystic ovary syndrome in China over the past decade. *Lancet Reg Health West Pac* 2022;25:100494.
- [4] Wang L, Zhou B, Zhao Z, Yang L, Zhang M, Jiang Y, et al. Body-mass index and obesity in urban and rural China: findings from consecutive nationally representative surveys during 2004–18. *Lancet* 2021;398(10294):53–63.
- [5] Azziz R, Carmina E, Chen Z, Dunaif A, Laven JSE, Legro RS, et al. Polycystic ovary syndrome. *Nat Rev Dis Primers* 2016;2:16057.
- [6] Andersen M, Glintborg D. Diagnosis and follow-up of type 2 diabetes in women with PCOS: a role for OGTT? *Eur J Endocrinol* 2018;179(3):D1–14.
- [7] Rotterdam ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group. Revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome (PCOS). *Hum Reprod* 2004;19(1):41–7.
- [8] Wang Q. Reconsideration of the three key scientific issues of TCM constitution and its prospect: speech at the 19th academic annual meeting of the TCM Constitution Branch, China Association of Chinese Medicine. *J Beijing Univ Tradit Chin Med* 2021;44(12):1061–6. Chinese.
- [9] Li L, Yao H, Wang J, Li Y, Wang Q. The role of Chinese medicine in health maintenance and disease prevention: application of Constitution Theory. *Am J Chin Med* 2019;47(3):495–506.
- [10] Wang J, Wang Q, Li L, Li Y, Zhang H, Zheng L, et al. Phlegm-dampness constitution: genomics, susceptibility, adjustment and treatment with traditional Chinese medicine. *Am J Chin Med* 2013;41(2):253–62.
- [11] Wang Y, Liu X, Xie L, Gao J, Ma H, Wang X, et al. Analysis of baseline characteristics of different TCM syndromes in infertile patients with polycystic ovary syndrome. *China J Tradit Chin Med Pharm* 2021;36(7):4318–24. Chinese.
- [12] Xu X, Hall J, Byles J, Shi Z. Dietary pattern is associated with obesity in older people in China: data from China Health and Nutrition Survey (CHNS). *Nutrients* 2015;7(9):8170–88.
- [13] Wang X, Wang J, Li L, Zheng Y, Bai M, Li Y, et al. Evaluation of interventive effect of WANG Qi's "Phlegm-dampness Constitution Conditioning Formula" in treating phlegm-dampness constitution. *Tianjin J Tradit Chin Med* 2019;36(04):319–21. Chinese.
- [14] Wu X, Wang CC, Cao Y, Li J, Li Z, Ma H, et al. Novel genetic risk and metabolic signatures of insulin signaling and androgenesis in the anovulation of polycystic ovary syndrome. *Engineering* 2023;23(4):103–11.
- [15] Wu X, Stener-Victorin E, Kuang H, Ma H, Gao J, Xie L, et al. Effect of acupuncture and clomiphene in Chinese women with polycystic ovary syndrome: a randomized clinical trial. *JAMA* 2017;317(24):2502–14.