The prescription patterns of traditional Chinese medicine for women with polycystic ovary syndrome in Taiwan
A nationwide population-based study
Mei-Jiun Lin, MD\textsuperscript{a}, Hsiao-Wei Chen, MD\textsuperscript{a,b}, Pi-Hua Liu, PhD\textsuperscript{c,d}, Wei-Jen Cheng, MD\textsuperscript{a,b}, Shun-Li Kuo, MD\textsuperscript{a,b}, Ming-Chen Kao, MD\textsuperscript{a,b,*}

Abstract
Polycystic ovary syndrome (PCOS) is a common endocrine disease of reproductive-age women, accounting for about 9% to 18% of all women in this age group. Hyperandrogenemia, oligomenorrhea, or amenorrhea or anovulation, and polycystic ovary morphology are the 3 main criteria used to diagnose PCOS currently. Substantial scientific evidence and consensus on treating Taiwanese PCOS was lacking. The aim of this study is to investigate the characteristics and utilization of traditional Chinese medicine (TCM) among Taiwanese women with PCOS.

The data used in this study were derived from the Longitudinal Health Insurance Database (LHID 2000 and LHID 2005). Demographic characteristics, TCM usage, the frequency, as well as average daily dose of Chinese herbal formulas and the single herbs prescribed for patients with PCOS, were analyzed. Chinese herbal formulas and the single herbs prescribed for PCOS women during 1999 to 2013 were extracted to build up Chinese Herbal Medicine prescription database.

In our study, 66.43\% (n=8205) women sought TCM treatment because of PCOS for infertility or menstrual disorders. The most commonly prescribed Chinese herbal formula was Jia-wei-xiao-yao-san (Supplemented Free Wanderer Powder). The most commonly prescribed single herb was Yi-mu-cao (Leonuri herba). Among top 20 Chinese herbal formulas, Si-wu-tang has the largest average daily dosage (9.60 g).

Our study identified the characteristics and prescription patterns of TCM for patients with PCOS in Taiwan. We may need do further longitudinal research for TCM and its long-term response for improvement of pregnancy rate and reduction of metabolic disease rate.

Abbreviations: CHM = Chinese herbal medicine, ICD-9 codes = International Classification of Diseases, 9th Revision, Clinical Modification, LHID = Longitudinal Health Insurance Database, NHI = National Health Insurance, PCOS = polycystic ovary syndrome, TCM = traditional Chinese medicine.

Keywords: complementary and alternative medicine, longitudinal health insurance database, polycystic ovary syndrome, traditional Chinese medicine
1. Introduction

Polycystic ovary syndrome (PCOS) is a common endocrine disease of reproductive-age women, accounting for about 9% to 18% of all women in this age group.[1] Hyperandrogenemia, oligomenorrhea or amenorrhea or anovulation, and polycystic ovary morphology are the main criteria used to diagnose PCOS currently. Clinical presentations of women with PCOS vary in different phenotypes, ages, ethnicities, and body weights. Obesity is a prominent feature of PCOS, occurring in 40% to 50% of these patients.[2] However, the average body mass index was much lower in Taiwanese PCOS women than Western women.[2] It is also important to evaluate the differences of PCOS women of various ages because of the clinical features and metabolic complications with the change of age.[3,4]

The treatment of PCOS is still challenging for physicians. The treatments on PCOS patients are mainly adopted depending on the symptoms.[5] PCOS treatment depends primarily on the desired clinical effect including infertility treatment, regulation of menstrual disturbances, alleviation of symptoms of hyperandrogenism, or obesity treatment. For women wishing to conceive, clomiphene still remains first-line therapy.[6] PCOS patients whose goal is not pregnancy are usually advised to use oral contraceptives, which could correct menstrual abnormalities and hyperandrogenemia.[6,7] However, treatment with oral contraceptives would increase the risk of venous thromboembolism.[8] Complementary and alternative therapies, such as traditional Chinese medicine (TCM), have beneficial effects of decreasing risk.

Previously, we have retrospectively collected and analyzed the patients with PCOS at the Taoyuan Chang Gung Memorial Hospital between 2004 and 2013, and the results demonstrated that tonifying recipes were the most common prescribed herbal formula.[9] Blood-regulating recipes and reconciliatory recipes were also commonly prescribed.[9] The limitations of that study were small size of database and that most patients came from North Taiwan. Substantial scientific evidence and consensus on treating Taiwanese PCOS was lacking. The aim of this study is to investigate the characteristics and utilization of TCM among Taiwanese women with PCOS. Therefore, we could design clinical trials to draw a conclusion of the therapeutic effects in the future.

2. Materials and Methods

2.1. Data source and study subjects

The data used in this study were derived from the Longitudinal Health Insurance Database (LHID 2000 and LHID 2005). The database consists of a random sample of 1 million subjects selected from the 22 million insured people of the National Health Insurance (NHI) Program in 2000 and 2005, respectively. The program covers approximately 99% of the entire population of Taiwan because the program is a single-payer system with mandatory enrollment.[10] The LHID contained all registration files and original claim data for reimbursement, as well as patient identification numbers, sociodemographic factors, diagnoses, prescription drugs dispensed, medical cost, medical care facilities, and specialties. The Ethics Committee of the Chang Gung Memorial Hospital waived the need for review board approval.

We included 12,351 individuals who had at least 2 clinic visits with diagnosis code of PCOS (International Classification of Diseases, 9th Revision, Clinical Modification [ICD-9] codes: 256,4) within 1 year from 1999 to 2013. All subjects were further divided into 2 groups: all TCM users (N = 10,934) and non-TCM users (N = 1417). To classify the treatment purpose, we specify all TCM users as 2 subgroups. One is TCM group (N = 8205), defined as patients with diagnosis of PCOS while they visited TCM clinics due to menstrual disorder or infertility problem. The other is “TCM other” group (N = 2729), defined as patients with diagnosis of PCOS and had least once visited TCM after the initial diagnosis of PCOS, but not for menstrual disorder or infertility problem. Non-TCM users (N = 1417) were defined as patients who never visited TCM clinics after the initial diagnosis (Fig. 1).

2.2. Statistical methods

Categorical data were presented as frequencies and percentages, and continuous variables were expressed as mean and standard deviation. Descriptive statistics were used to illustrate demographics and major disease categories in TCM and non-TCM users. χ² and t tests were used to evaluate differences in the distribution of demographic, clinical characteristics, and major disease categories between the TCM and Non-TCM groups. A P value of <0.05 was considered statistically significant. All analyses were performed using SAS version 9.4 (SAS Institute Inc. Cary, NC).

3. Results

According to the age distribution, younger patients were more likely to seek TCM treatment. Most of the patients went to regional hospitals. Because Taiwan’s population is mostly distributed in the North, so the patients are mostly in the North, followed by South Taiwan. Furthermore, TCM users had more outpatient visits per year than non-TCM users (P < .0001). Details on demographic distribution of TCM users and non-users are provided in Table 1.

In TCM, there was no “PCOS” medical terminology, but with clinical symptoms such as amenorrhea, oligomenorrhea, irregular menstruation, or infertility. Therefore, we use Western medical diagnostic methods (ICD-9) for disease classification. We analyzed the distribution of major disease categories/diagnosis in TCM and non-TCM users among polycystic ovarian syndrome patients, which showed the major disease category for PCOS patients were endocrine, nutritional, and metabolic disease, followed by disease of genitourinary system. (Table 2)

In Taiwan, there are 2 types of Chinese herbal medicine (CHM): herbal formulas and single herbs. Herbal formulas are mixtures of several herbal medicines and had specific indications for TCM use. Both herbal formulas and single herbs are all processed into concentrated powders. To investigate the prescription patterns of the Chinese herbal products for PCOS patients with infertility or menstrual disorders, we conducted a comprehensive analysis and identified 20 most commonly prescribed Chinese herbal formula (Table 3) and 10 single herbs (Table 4). The top 20 frequently used herbal formulas with its constituents and indication in TCM use are showed in Table 5. The most commonly prescribed Chinese herbal formula was Jia-xue-yao-san (Supplemented Free Wanderer Powder), followed by Yi-mu-cao (Herba Leonuri), followed by Xiang-fu (Cyperi Rhizoma) and Tu-si-zi...
(Cuscutae Semen). Among top 20 Chinese herbal formulas, Si-wu-tang has the largest average daily dosage (9.60g).

Owing to the clinical features and metabolic complications of PCOS with change of age,[11,12] we grouped these patients to analyze their medication.[9] The results showed Jia-wei-xiao-yao-san, Wen-jing-tang, Gui-zhi-fu-ling-wan, Dang-gui-shao-yao-san, and Shao-fu-zhu-yu-tang were the most commonly prescribed Chinese herbal formulas at different age groups (Fig. 2). But the prescription pattern had no significant difference between different age groups.

4. Discussion

PCOS is a heterogeneous and complex disorder that has both adverse reproductive and metabolic implications for affected women.[13] Many western medical therapies have been used to manage PCOS, such as oral contraceptives, insulin sensitizers, and laparoscopic ovarian drilling. CHMs have been suggested as an alternative approach for women with PCOS.[14] This is a large-scale survey of Chinese herbal prescriptions and herbs used in the treatment of women with PCOS.

In Taiwan, the NHI provides coverage for >98% of the population, and the prescription for CHM and western medicine is equally covered. Therefore, patients are free to choose different treatments. According to Table 1, we found younger patients were more likely to seek for TCM treatment. In addition to the treatment of western medicine, TCM offers another treatment option, which may have fewer side effects.

In TCM, the major therapeutic principles of PCOS include tonifying the kidney, dispersing stagnated liver Qi, regulating blood, and clearing damp and resolving phlegm.[19] Because every prescription has their major effects matching the therapeutic principles, we analyze the prescriptions and classify their major effects into different categories. The most common category was dispersing stagnated liver Qi, which may be caused by modern social or family pressures. The common
category was followed by dispersing stagnated liver Qi, tonifying the kidney, qi/blood and regulating blood. Therefore, in Table 3, the top 6 drugs are Jia-Wei-xiao-yao-san, Wen-jing-tang, Gui-zhi-fu-ling-wan, Ang-gui-shao-yao-san, Shao-fu-ling-wan, and Dang-gui-shao-yao-san. The top 10 most common prescribed single herbs are illustrated in Table 4, with top 1st drug being Yi-mu-cao, which was reported to have anti-inflammatory activity, reducing prostaglandin synthase-2 concentration in uterine smooth muscle and increasing the serum progesterone level. Xiang-fu, the second commonly used drugs, also has antioxidative potency and free radical scavenging activity. The third common prescribed drug is Tu-si-zi, which improves ovarian endocrine dysfunction and increases estrogen receptor expression in the hippocampus, hypothalamus, and pituitary glands, as well

### Table 1

Demographic and clinical characteristics of TCM and non-TCM uses in patients with polycystic ovarian syndrome.

| Characteristics | TCM (N = 8205) | TCM other (N = 2729) | Non-TCM (N = 1417) | P |
|-----------------|---------------|----------------------|-------------------|---|
| Age group, y    |               |                      |                   |   |
| 18–25           | 3111 (37.92)  | 864 (31.66)          | 483 (34.09)       | <.0001 |
| 26–30           | 2501 (30.48)  | 719 (26.35)          | 356 (25.12)       |   |
| 31–35           | 1724 (21.01)  | 618 (22.66)          | 339 (23.92)       |   |
| 36–40           | 627 (7.64)    | 322 (11.18)          | 151 (10.66)       |   |
| 41–45           | 212 (2.58)    | 159 (5.83)           | 62 (4.38)         |   |
| 46–50           | 30 (0.37)     | 47 (1.72)            | 26 (1.83)         |   |
| Institution class |              |                      |                   |   |
| Medical Center  | 1783 (21.73)  | 658 (24.11)          | 324 (22.87)       | .1226 |
| Regional Hospitals | 3041 (37.06) | 934 (34.22)          | 555 (39.17)       |   |
| District hospitals | 1425 (17.37) | 495 (18.14)          | 236 (16.65)       |   |
| Clinics         | 1956 (23.84)  | 642 (23.53)          | 302 (21.31)       |   |
| Regional division |              |                      |                   |   |
| Northern        | 3835 (46.74)  | 1442 (52.84)         | 836 (59.00)       | <.0001 |
| Central         | 1730 (21.08)  | 451 (16.53)          | 171 (12.07)       |   |
| Southern        | 2483 (30.26)  | 789 (28.91)          | 382 (26.96)       |   |
| Eastern         | 136 (1.66)    | 38 (1.36)            | 26 (1.83)         | .31 |
| Outlying islands | 21 (0.26)    | 9 (0.33)             | 2 (0.14)          |   |
| Outpatient visits, y^4 | 19.51 ± 12.21 | 17.53 ± 11.05 | 11.89 ± 9.77 | <.0001 |

TCM = traditional Chinese medicine.

1. All TCM = patients with diagnosis of PCOS and had least once visited TCM after the initial diagnosis of PCOS.

2. TCM = patients with diagnosis of PCOS while them visited TCM clinics due to menstrual disorder or infertility problem.

3. TCM other = patients with diagnosis of PCOS and had least once visited TCM after the initial diagnosis of PCOS, but not for menstrual disorder or infertility problem.

4. Non-TCM = patients who never visited TCM clinics after the initial diagnosis.

P value between TCM users and non-TCM users.

In older women, metabolic disturbances and obesity are the major problem. We usually prescribe Wen-dan-tang to clear damp and resolve phlegm from obese patients in TCM classics. However, in Table 3, Wen-dan-tang is not one of the top categories in this study. One reason could be that obese female population is relatively small in Taiwan. In addition to this, in the top 20 commonly used drugs, Long-dan-xie-gan-tang belongs to clearing away heat purge pathogenic fire category, which is not within the 4 major therapeutic principles, but still common for PCOS patients. Besides, in other animal experiment, Long-dan-xie-gan-tang could increase corpora lutea and corpora albicantia, whereas cystic follicles and secondary follicles numbers were decreased.

Table 4 shows top 10 most common prescribed single herbs and categorizes their major effects into different categories. Most of them belong to the category of promoting blood circulation and removing blood stasis, such as Yi-mu-cao, Dan-shen, Yan-hu-su, and Hong-hua. The others belong to tonifying the kidney, such as Tu-si-zi, Xu-duan, Nu-zhen-zi, and Du-zhong. The top first drug is Yi-mu-cao, which was reported to have antioxidative activity and could treat dysmenorrhea by relaxing uterine spasms, decreasing inflammation, reducing prostagaldin F2α, and prostagladin synthase-2 concentration in uterine smooth muscle and increasing the serum progesterone level. The third common prescribed drug is Tu-si-zi, which improves ovarian endocrine dysfunction and increases estrogen receptor expression in the hippocampus, hypothalamus, and pituitary glands, as well.
Table 2
Distribution of major disease categories/diagnosis in TCM and non-TCM users among polycystic ovarian syndrome patients.

| Major disease category/diagnosis                          | ICD-9-CM Code range | All TCM (N = 10,934) N (%) | Non-TCM (N = 1417) N (%) |
|----------------------------------------------------------|---------------------|----------------------------|--------------------------|
| Infection and parasitic diseases                         | 001–139             | 7072 (64.29)               | 611 (43.12)              |
| Neoplasms                                                | 140–239             | 5104 (46.68)               | 454 (32.04)              |
| Endocrine, nutritional and metabolic diseases            | 240–279             | 10779 (98.58)              | 1379 (97.32)             |
| Mental disorders                                         | 290–319             | 3211 (29.37)               | 225 (15.88)              |
| Anxiety state unspecified                               | 300                 | 59 (0.54)                  | 4 (0.28)                 |
| Neurosis, NOS                                            | 300.9               | 356 (3.26)                 | 21 (1.48)                |
| Insomnia, transient                                     | 307.41              | 171 (1.56)                 | 11 (0.78)                |
| Sleep disorder persistent                               | 307.42              | 393 (3.59)                 | 28 (1.98)                |
| Diseases of nervous system and sense organs             | 320–389             | 8466 (77.61)               | 784 (55.33)              |
| Diseases of circulatory system                          | 390–459             | 3503 (32.86)               | 307 (21.67)              |
| Diseases of respiratory system                          | 460–519             | 10344 (94.60)              | 1175 (82.92)             |
| Diseases of digestive system                            | 520–579             | 10351 (94.67)              | 1190 (83.98)             |
| Diseases of genitourinary system                        | 580–629             | 10746 (96.28)              | 1291 (91.11)             |
| Endometriosis                                            | 617                 | 73 (0.67)                  | 1 (0.07)                 |
| Infertility                                              | 628                 | 295 (2.70)                 | 16 (1.13)                |
| Disorders of menstruation and other abnormal bleeding from female genital tract | 626 | 968 (8.04) | 20 (1.41) |
| Dysmenorrhea                                             | 625.5               | 2901 (26.57)               | 146 (10.30)              |
| Premenstrual tension syndromes                          | 625.4               | 576 (5.27)                 | 8 (0.56)                 |
| Diseases of skin and subcutaneous tissue                | 680–709             | 9299 (85.05)               | 964 (68.03)              |
| Diseases of musculoskeletal system and connective tissue | 710–739             | 7895 (72.21)               | 583 (41.14)              |
| Symptoms, signs, and ill-defined conditions             | 780–799             | 9659 (90.17)               | 984 (69.44)              |
| Insomnia                                                 | 780.5               | 507 (4.64)                 | 5 (0.35)                 |
| Injury and poisoning                                     | 800–999             | 8155 (74.58)               | 623 (43.97)              |
| Others‡                                                  | 8555 (78.24)        | 865 (61.04)                |                          |
| Total§                                                   | 113,403             | 11,435                     |                          |

ICD-9-CM codes = International Classification of Diseases, 9th Revision, Clinical Modification, TCM = traditional Chinese medicine.

1 All TCM = patients with diagnosis of PCOS and had least once visited TCM after the initial diagnosis of PCOS.

2 Non-TCM = patients who never visited TCM clinics after the initial diagnosis.

3 Others include ICD-9-CM code range 280–289, 630–677, 740–759, 760–779, and missing/error data.

4 Sum up frequency of infection and parasitic diseases, neoplasms, endocrine, nutritional and metabolic diseases, mental disorders, diseases of nervous system and sense organs, diseases of circulatory system, diseases of respiratory system, diseases of digestive system, diseases of genitourinary system, diseases of skin and subcutaneous tissue, diseases of musculoskeletal system and connective tissue, symptoms, signs, and ill-defined conditions, and injury and poisoning, and others.

Table 3
The top 20 most herbal formulas for patients with polycystic ovarian syndrome from 1999 to 2013 in Taiwan.

| Herbal formulae                  | English name                          | TCM (N = 8205) N (%) | Frequency (%) N = 160,857 | Average daily dosage, g |
|---------------------------------|---------------------------------------|----------------------|---------------------------|-------------------------|
| Jia-wen-xia-yao-san             | Supplemented Free Wanderer Powder     | 3174 (38.68%)        | 15,311 (9.52%)            | 6.05                    |
| Wen-jing-tang                   | Menstrual-Warming Decoction           | 2338 (28.49%)        | 9482 (5.89%)              | 6.50                    |
| Gui-zhi-fu-ling-wan             | Cinnamon Twig and Poria Pill         | 2289 (27.9%)         | 8938 (5.56%)              | 6.79                    |
| Dong-gui-shao-yao-san           | Chinese Angelica and Peony Powder    | 2089 (25.46%)        | 7746 (4.82%)              | 6.23                    |
| Shao-fu-zhu-yu-tang             | Lesser Abdomen Stasis-Expelling Decoction | 1652 (20.13%)   | 5393 (3.35%)              | 7.36                    |
| Zou-gui-wan                     | Left Restoring [Kidney Yin] Pill     | 1019 (12.42%)        | 4350 (2.7%)               | 5.20                    |
| Gui-qi-tang                     | Spleen-Returning Decoction           | 1192 (14.53%)        | 3513 (2.18%)              | 6.19                    |
| Guo-qi-yin                      | Overdue Beverage                     | 1153 (14.05%)        | 3506 (2.18%)              | 6.36                    |
| You-gui-wan                    | Right-Reducing [Life Gate] Pill      | 847 (10.32%)         | 3276 (2.04%)              | 8.16                    |
| Tao-hong-si-xu-tang             | Peach Kernel and Carthamus Four Agents Decoction | 1050 (12.8%)  | 3244 (2.02%)              | 7.33                    |
| Xi-xiao-gui-jiao-al-tang        | Chuaangdong, Chinese Angelica, Ass Hidz Glue, and Mugwort Decoction | 1088 (13.26%)    | 3105 (1.93%)              | 8.32                    |
| Liu-wi-dai-huang-wan            | Six-Ingredient Rehmannia Pill        | 953 (11.61%)         | 3075 (1.91%)              | 5.39                    |
| Xiao-yao-san                    | Free Wanderer Powder                 | 924 (11.26%)         | 3039 (1.99%)              | 5.80                    |
| Xue-fu-hu-yu-tang               | House of Blood Stasis-Expelling Decoction | 931 (11.35%)    | 2771 (1.72%)              | 5.35                    |
| Ma-Zi-ren-wan                  | Cannabis Fruit Pill                  | 589 (7.18%)          | 2730 (1.7%)               | 4.52                    |
| Si-wu-tang                      | Four Agents Decoction                | 780 (9.51%)          | 2400 (1.49%)              | 9.60                    |
| Tao-he-cheng-qi-tang           | Peach Kernel Qi-Coordinating Decoction | 617 (7.52%)     | 2360 (1.47%)              | 4.30                    |
| Neu-ke-bai-zu-ren-wan           | Arborenae Seed Pill                  | 745 (9.08%)          | 2249 (1.4%)               | 4.68                    |
| Wen-dan-tang                    | Gallbladder-Warming Decoction        | 605 (7.37%)          | 2149 (1.34%)              | 4.98                    |
| Long-dan-xue-gan-tang           | Gentian Liver-Draining Decoction     | 500 (6.09%)          | 1700 (1.06%)              | 3.57                    |

T = total frequency. TCM = traditional Chinese medicine.

1 TCM = patients with diagnosis of PCOS while they visited TCM clinics due to menstrual disorder or infertility problem.
Table 4

The most common prescribed single herbs in the treatment of polycystic ovarian syndrome.

| Name                  | English name | TCM (N = 8205) | N (%)   | Frequency (229,725) | Average daily dosage, g |
|-----------------------|--------------|----------------|---------|---------------------|-------------------------|
| Yi-mu-cao             | Leonurus (Leonori herba) | 2689 (32.21%) | 12,496 (5.44%) | 1.85 |
| Xiang-fu              | Cyparissus (Cyparis zonata) | 2316 (28.25%) | 10,562 (4.64%) | 1.64 |
| Tu-si-zhi             | Cuscuta (Cuscutae semen) | 1788 (21.79%) | 9115 (3.97%) | 1.75 |
| Dan-shen              | Salvia (Salviae Millionariae radix) | 1623 (19.78%) | 6011 (2.62%) | 1.76 |
| Da-huang              | Rubraria (Rubiae Radix et Rhizoma) | 973 (11.86%) | 5031 (2.19%) | 0.67 |
| Yan-hu-suo            | Corydalis (Corydalis rhizoma) | 1521 (18.54%) | 4793 (2.09%) | 1.78 |
| Xu-duan               | Dipsacus (Dipsaci radix) | 1155 (14.08%) | 4127 (1.8%) | 1.65 |
| Hong-hua              | Carthamus (Carthami flos) | 1201 (14.64%) | 3977 (1.73%) | 2.02 |
| Nu-zen-zi             | Ligusturum (Ligustri Lucidi fructus) | 1103 (13.44%) | 3924 (1.71%) | 1.63 |
| Du-zhong              | Eucommia (Eucommiae cortex) | 1086 (13.24%) | 3756 (1.64%) | 1.21 |

T = total frequency. TCM = traditional Chinese medicine.
* = defined as patients with diagnosis of PCOS while visited TCM clinics due to menstrual disorder or infertility problem.

Table 5

The top 20 most frequently used herbal formula with its constituents and indication in TCM use for polycystic ovary syndrome.

| Name                  | Constituents | TCM (N = 8205) | N (%)   | Frequency (229,725) | Average daily dosage, g |
|-----------------------|--------------|----------------|---------|---------------------|-------------------------|
| Jia-wei-xia-yao-san   | Angelicae sinensis (Dang-gui), Poriae cocos (Fu-ling), Gardeniae jasminoides (Zhi-zi), Mentha haplocalyx (Bo-he), Paeoniae alba (Bao-shao), Puerariae radix (Cao-yao), Poriae cocos (Fu-ling), Angelicae sinensis (Shu-duan), Zingiber officinalis (Ren-shao), Poriae cocos (Fu-ling), Poriae cocos (Fu-ling) | 20,803 (25.18%) | 72,258 (31.5%) | 3.57 |
| Wen-jing-tang         | Evodia rutaecarpa (Wu-zhu-yu), Ginseng Radix (Ren-shen), Cinnamomi ramulus (Gui-zhi), Ligustici chuanxiong (Chuan-xiong), Zingiber officinalis (Ren-shao), Poriae cocos (Fu-ling), Angelicae sinensis (Shu-duan), Poriae cocos (Fu-ling), Poriae cocos (Fu-ling) | 16,308 (19.88%) | 52,927 (23.4%) | 2.53 |
| Gui-zhi-tu-ling-wan   | Cinnamomi ramulus (Gui-zhi), Poriae cocos (Fu-ling), Poriae cocos (Fu-ling), Poriae cocos (Fu-ling), Poriae cocos (Fu-ling), Poriae cocos (Fu-ling), Poriae cocos (Fu-ling) | 11,033 (13.44%) | 39,247 (17.4%) | 2.13 |
| You-gui-wan           | Rehmanniae Radix Praeparata (Shu-di-huang), Dioscoreae Rhizoma (Shan-yao), Carthami Flos (Hong-hua), Poriae cocos (Fu-ling), Angelicae sinensis (Dang-gui), Zingiber officinalis (Ren-shao), Poriae cocos (Fu-ling), Poriae cocos (Fu-ling), Poriae cocos (Fu-ling) | 9,731 (11.86%) | 29,857 (13.3%) | 1.57 |
| Gui-pi-tiang          | Ginseng Radix (Ren-shen), Astragalus radix (Huang-qiao), Atractylodis macrocephalae (Bai-zhu), Angelicae sinensis (Dang-gui), Zingiber officinalis (Ren-shao), Poriae cocos (Fu-ling), Poriae cocos (Fu-ling), Poriae cocos (Fu-ling), Poriae cocos (Fu-ling) | 8,125 (9.93%) | 24,754 (11.1%) | 1.29 |
| Guo-qi-yin            | Rehmanniae Radix Praeparata (Shu-di-huang), Paeoniae alba (Bao-shao), Angelicae sinensis (Dang-gui), Cyparis (Cyparis zonata), Angelicae sinensis (Dang-gui), Zingiber officinalis (Ren-shao), Poriae cocos (Fu-ling), Poriae cocos (Fu-ling), Poriae cocos (Fu-ling) | 7,531 (9.21%) | 21,797 (9.5%) | 1.16 |
| You-gui-wan           | Rehmanniae Radix Praeparata (Shu-di-huang), Dioscoreae Rhizoma (Shan-yao), Zingiber officinalis (Ren-shao), Poriae cocos (Fu-ling), Paeoniae alba (Bao-shao), Poriae cocos (Fu-ling), Poriae cocos (Fu-ling), Poriae cocos (Fu-ling), Poriae cocos (Fu-ling) | 6,925 (8.41%) | 19,854 (8.7%) | 1.08 |
| Tao-hong-si-wu-tang   | Angelicae sinensis (Dang-gui), Ligustici chuanxiong (Chuan-xiong), Paeoniae alba (Bao-shao), Zingiber officinalis (Ren-shao), Poriae cocos (Fu-ling), Poriae cocos (Fu-ling), Poriae cocos (Fu-ling), Poriae cocos (Fu-ling), Poriae cocos (Fu-ling) | 6,325 (7.81%) | 18,754 (8.3%) | 1.03 |

(continued)
| Name                        | Constituents                                                                 | Indication in TCM use                                                                 |
|-----------------------------|------------------------------------------------------------------------------|--------------------------------------------------------------------------------------|
| Liu-wei-di-huang-wan        | *Rehmanniae Radix Praeparata* (Shu-di-huang), *Corni Fructus* (Shan-zhu-yu), *Dioscoreae Rhizaoma* (Shan-yao), *Alismatis Rhizaoma* (Ze-xie), *Poriae cocos* (Fu-ling), *Paeonia suffruticosa* radices (Nu-dan-pi) | Lower back soreness and weakness, light headedness, vertigo, tinnitus, diminished hearing, night sweats, spontaneous and nocturnal emissions. |
| Xiao-yao-san                | *Bupleurum chinense* (Chai-hu), *Angelicae sinensis* (Dang-gui), *Paeoniae alba* (Zhi-shao), *Atractylodis macropoda* (Bai-zhu), *Poriae cocos* (Fu-ling), *Glycyrrhizae uralensis* (Gan-cao), *Zingiberis officinalis* recens (Seng-jiang), *Mentha haplocalyx* (Bo-he) | Irritability, lower abdominal pressure, painful urination, increased menstrual flow or uterine blood. |
| Xue-fu-zhu-yu-tang          | *Angelicae sinensis* (Dang-gui), *Rehmanniae Radix* (Sheng-di-huang), *Persicae Semen* (Tao-ren), *Carthami Flos* (Hong-hua), *Aurantii Fructus* (Zhi-qiao), *Paeoniae radices* rubra (Ch-shao), *Bupleurum chinense* (Chai-hu), *Glycyrrhizae uralensis* (Gan-cao), *Platycodonis Radix* (Jie-geng), *Ligustici chuanxiong* (Chuan-xiong), *Achyranthis Bidentatae Radix* (Niu-xi) | Depression or low spirits, insomnia, restless sleep, irritability, extreme mood swings. |
| Ma-Zi-ren-wan               | *Cannabis Fructus* (Ma-zi-zen), *Paeoniae alba* (Bao-shao), *Aurantii Fructus Immaturus* (Zhi-shi), *Rhei Radix et Rhizoma* (Da-huang), *Magnoliae Officinalis Cortex* (Hou-po), *Ameniacea Semen* (Kung-ren) | Constipation with hard stool that is difficult to expel, frequent urination. |
| Si-wu-tang                  | *Angelicae sinensis* (Dang-gui), *Ligustici chuanxiong* (Chuan-xiong), *Paeoniae alba* (Bao-shao), *Rehmanniae Radix Praeparata* (Shu-di-huang) | Dizziness, lusterless complexion and nails, muscle tension, insomnia, irregular menses with little flow, lower abdominal pain. |
| Tao-he-cheng-qi-tang        | *Persicae Semen* (Tao-ren), *Rhei Radix et Rhizoma* (Da-huang), *Cinnamomi ramulus* (Gui-zhi), *Glycyrrhizae uralensis* (Gan-cao), *Natrii Sulphas* (Mang-xia) | Acute lower abdominal pain, night fevers, delirious speech, irritability, restlessness, and dysmenorrhea or amenorrhea. |
| Neu-ke-bai-zi-ren-wan       | *Phytophalae Semen* (Bai-zi-ren), *Rehmanniae Radix Praeparata* (Shu-di-huang), *Achyranthis Bidentatae Radix* (Niu-xi), *Selaginellae Herba* (Juan-bai), *Dipsaci Radix* (Xu-duan), *Lycopyli Herba* (Ze-lan) | Insomnia with irritability, palpitations, night sweat, constipation, weak memory. |
| Wen-dan-tang                | *Pinelliae temnata* (Ban-xia), *Ophiocarpus Tonicum* Rubrum (Ju-hong), *Poriae cocos* (Fu-ling), *Glycyrrhizae uralensis* (Gan-cao), *Bumbusea Caulis in Taenia* (Zhi-shi), *Aurantii Fructus Immaturus* (Zhi-shi), *Zingiberis officinalis* recens (Seng-jiang), *Jujubae Fruites* (Da-zao) | Dizziness, vertigo, nausea and vomiting, insomnia, dream-disturbed sleep, palpitations, anxiety, hunger, seizures. |
| Long-dan-xie-gan-tang       | *Gentianae Radix* (Long-dan-cao), *Gardeniae jasminoides* (Zhi-qí), *Scutellariae Radix* (Huang-qin), *Bupleurum chinense* (Chai-hu), *Rehmanniae Radix* (Sheng-di-huang), *Alismatis Rhizaoma* (Ze-xie), *Angelicae sinensis* (Dang-gui), *Platycodonis Semen* (Che-qian-zì), *Akebias Trifoliatae Caulis* (Mu-tong), *Glycyrrhizae uralensis* (Gan-cao) | Headache, dizziness, irritability, eczema, intercostal neuralgia, conjunctivitis, otitis, hypertension, herpes zoster. |

TCM = traditional Chinese medicine.

**Figure 2.** The top 5 most prescribed drugs for polycystic ovary syndrome stratified by age group.
Investigation: Lin Mei-Jiun, Chen Hsiao-Wei, Kao Ming-Chen
Methodology: Liu Pi-Hua, Kao Ming-Chen
Software: Liu Pi-Hua, Kao Ming-Chen
Supervision: Cheng Wei-Jen, Kuo Shun-Li, Kao Ming-Chen
Validation: Cheng Wei-Jen, Kuo Shun-Li
Writing – original draft: Lin Mei-Jiun, Chen Hsiao-Wei
Writing – review & editing: Cheng Wei-Jen, Kuo Shun-Li, Kao Ming-Chen

Formal analysis: Pi Hua Liu.
Methodology: Wei Jen Cheng, Shun Li Kuo.
Writing – original draft: Mei Jiu Lin, Hsiao Wei Chen.
Writing – review & editing: Ming Chen Kao.

References

[1] March WA, Moore VM, Willson KJ, et al. The prevalence of polycystic ovary syndrome in a community sample assessed under contrasting diagnostic criteria. Hum Reprod 2010;25:544–51.

[2] Hsu MI. Clinical characteristics in Taiwanese women with polycystic ovary syndrome. Clin Exp Reprod Med 2015;42:86–93.

[3] Pasquali R, Gambineri A. Polycystic ovary syndrome: a multifaceted disease from adolescence to adult age. Ann N Y Acad Sci 2006;1092:158–74.

[4] Cheung LP, Ma RC, Lam PM, et al. Cardiovascular risks and metabolic syndrome in Hong Kong Chinese women with polycystic ovary syndrome. Hum Reprod 2008;23:1431–8.

[5] Liu Y, Chen Y. Fat mass and obesity associated gene polymorphism and the risk of polycystic ovary syndrome: a meta-analysis. Iran J Public Health 2017;46:4–11.

[6] Bednarska S, Siejka A. The pathogenesis and treatment of polycystic ovary syndrome: What’s new? Adv Clin Exp Med 2017;26:359–47.

[7] Legro RS, Arslanian SA, Ehrmann DA, et al. Diagnosis and treatment of polycystic ovary syndrome: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab 2013;98:4565–92.

[8] Soares GM, Vieira CS, de Paula Martins W, et al. Metabolic and cardiovascular impact of oral contraceptives in polycystic ovary syndrome. Int J Clin Pract 2009;63:160–9.

[9] Chen HW, Chiang WJ, Chen CL, et al. Characteristics and prescription patterns of traditional Chinese medicine in polycystic ovary syndrome. Journal of Chengdu University of TCM 2015;38:120–3.

[10] National Health Insurance Administration, Ministry of Health and Welfare, Taiwan, R.O.C. (2014). National Health Insurance Annual Report 2014-2015.

[11] Liang SJ, Hsu CS, Tzeng CR, et al. Clinical and biochemical presentation of polycystic ovary syndrome in women between the ages of 20 and 40. Hum Reprod 2011;26:1443–9.

[12] Hsu MI. Changes in the PCOS phenotype with age. Steroids 2013;78:761–6.

[13] Dumesic DA, Oberfield SE, Stener-Victorin E, et al. Scientific statement on the diagnostic criteria, epidemiology, pathophysiology, and molecular genetics of polycystic ovary syndrome. Endocr Rev 2015;36:487–525.

[14] Zhou K, Zhang J, Xu L, et al. Chinese herbal medicine for subfertile women with polycystic ovarian syndrome. Cochrane Database of Syst Rev 2016;CD007535.

[15] Sched V, Bensky D, Ellis A, et al. Clinical and biochemical presentation of polycystic ovary syndrome in women between the ages of 20 and 40. Hum Reprod 2011;26:1443–9.

[16] Hsu MI. Changes in the PCOS phenotype with age. Steroids 2013;78:761–6.

[17] Dumesic DA, Oberfield SE, Stener-Victorin E, et al. Scientific statement on the diagnostic criteria, epidemiology, pathophysiology, and molecular genetics of polycystic ovary syndrome. Endocr Rev 2015;36:487–525.

[18] Zhou K, Zhang J, Xu L, et al. Chinese herbal medicine for subfertile women with polycystic ovarian syndrome. Cochrane Database of Syst Rev 2016;CD007535.

[19] Sched V, Bensky D, Ellis A, et al. Clinical and biochemical presentation of polycystic ovary syndrome in women between the ages of 20 and 40. Hum Reprod 2011;26:1443–9.

[20] Hsu MI. Changes in the PCOS phenotype with age. Steroids 2013;78:761–6.

[21] Dumesic DA, Oberfield SE, Stener-Victorin E, et al. Scientific statement on the diagnostic criteria, epidemiology, pathophysiology, and molecular genetics of polycystic ovary syndrome. Endocr Rev 2015;36:487–525.

[22] Zhou K, Zhang J, Xu L, et al. Chinese herbal medicine for subfertile women with polycystic ovarian syndrome. Cochrane Database of Syst Rev 2016;CD007535.

[23] Sched V, Bensky D, Ellis A, et al. Clinical and biochemical presentation of polycystic ovary syndrome in women between the ages of 20 and 40. Hum Reprod 2011;26:1443–9.

[24] Hsu MI. Changes in the PCOS phenotype with age. Steroids 2013;78:761–6.

[25] Dumesic DA, Oberfield SE, Stener-Victorin E, et al. Scientific statement on the diagnostic criteria, epidemiology, pathophysiology, and molecular genetics of polycystic ovary syndrome. Endocr Rev 2015;36:487–525.

[26] Zhou K, Zhang J, Xu L, et al. Chinese herbal medicine for subfertile women with polycystic ovarian syndrome. Cochrane Database of Syst Rev 2016;CD007535.

[27] Sched V, Bensky D, Ellis A, et al. Clinical and biochemical presentation of polycystic ovary syndrome in women between the ages of 20 and 40. Hum Reprod 2011;26:1443–9.

[28] Hsu MI. Changes in the PCOS phenotype with age. Steroids 2013;78:761–6.

[29] Dumesic DA, Oberfield SE, Stener-Victorin E, et al. Scientific statement on the diagnostic criteria, epidemiology, pathophysiology, and molecular genetics of polycystic ovary syndrome. Endocr Rev 2015;36:487–525.

[30] Zhou K, Zhang J, Xu L, et al. Chinese herbal medicine for subfertile women with polycystic ovarian syndrome. Cochrane Database of Syst Rev 2016;CD007535.

[31] Sched V, Bensky D, Ellis A, et al. Clinical and biochemical presentation of polycystic ovary syndrome in women between the ages of 20 and 40. Hum Reprod 2011;26:1443–9.

[32] Hsu MI. Changes in the PCOS phenotype with age. Steroids 2013;78:761–6.

[33] Dumesic DA, Oberfield SE, Stener-Victorin E, et al. Scientific statement on the diagnostic criteria, epidemiology, pathophysiology, and molecular genetics of polycystic ovary syndrome. Endocr Rev 2015;36:487–525.

[34] Zhou K, Zhang J, Xu L, et al. Chinese herbal medicine for subfertile women with polycystic ovarian syndrome. Cochrane Database of Syst Rev 2016;CD007535.

[35] Sched V, Bensky D, Ellis A, et al. Clinical and biochemical presentation of polycystic ovary syndrome in women between the ages of 20 and 40. Hum Reprod 2011;26:1443–9.

[36] Hsu MI. Changes in the PCOS phenotype with age. Steroids 2013;78:761–6.

[37] Dumesic DA, Oberfield SE, Stener-Victorin E, et al. Scientific statement on the diagnostic criteria, epidemiology, pathophysiology, and molecular genetics of polycystic ovary syndrome. Endocr Rev 2015;36:487–525.

[38] Zhou K, Zhang J, Xu L, et al. Chinese herbal medicine for subfertile women with polycystic ovarian syndrome. Cochrane Database of Syst Rev 2016;CD007535.
[21] Hu X, Lu H, Deng YL, et al. Effect of rat medicated serum containing Zuo Gui Wan and/or You Gui Wan on the differentiation of stem cells derived from human first trimester umbilical cord into oocyte-like cells in vitro. Evidence Based Complement Alternat Med 2015;2015: Article ID 825805.

[22] Dong L, Tan Y, Ping YJ, et al. Comparative study of different therapeutic methods on autoimmune premature ovarian failure in mice. Zhong Xi Yi Jie He Xue Bao 2010;8:86–9.

[23] Lee JC, Pak SC, Lee SH, et al. The effect of herbal medicine on nerve growth factor in estradiol valerate-induced polycystic ovaries in rats. Am J Chin Med 2003;31:885–95.

[24] Shang XF, Pan H, Wang XZ, et al. Leonurus japonicus Houtt.: ethnopharmacology, phytochemistry and pharmacology of an important traditional Chinese medicine. J Ethnopharmacol 2014;152:14–32.

[25] Jin RM, Chen ZS, Chen ZX, et al. Effects of motherwort on dysmenorrhea. The Chinese Pharmaceutical Association 2001;21:90.

[26] Lee CH, Hwang DS, Kim HG, et al. Protective effect of Cypri rhizoma against 6-hydroxydopamine-induced neuronal damage. J Med Food 2010;13:564–71.

[27] Ke J, Duan R. Effects of flavonoids from semen cuscutae on the hippocampal-hypothalamic-pituitary-ovarian sex hormone receptors in female rats exposed to psychological stress. Clin Exp Obstet Gynecol 2013;40:271–4.

[28] Agha-Hosseini M, Kashani L, Aleyaseen A, et al. Crocus sativus L. (saffron) in the treatment of premenstrual syndrome: a double-blind, randomised and placebo-controlled trial. BJOG 2008;115:515–9.

[29] Khodakarami N, Moatar F, Gharibi A, et al. The effect of an Iranian herbal drug on primary dysmenorrhea: a clinical controlled trial. J Midwifery Womens Health 2009;54:401–4.