Chinese Herbal Products for Female Infertility in Taiwan

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Abstract: Female infertility and low birth rate are significant public health issues with profound social, psychological, and economic consequences. Some infertile women resort to conventional, complementary, or alternative therapies to conceive. The aim of this study was to identify the Chinese herbal products (CHPs) most commonly used for female infertility in Taiwan.

The usage of traditional Chinese medicine (TCM) and the frequency of CHP prescriptions to infertile women were determined based on a nationwide 1-million randomly sampled cohort of National Health Insurance Research Database beneficiaries. Descriptive statistics and multiple logistic regression analysis were employed to estimate the adjusted odds ratio (aOR) for CHP usage and potential risk factors.

In total, 8766 women with newly diagnosed infertility were included in this study. Of those, 8430 (96.17%) had sought TCM treatment in addition to visiting the gynecologist. We noted that female infertility patients with risk factors (e.g., endometriosis, uterine fibroids, or irregular menstrual cycle) were more likely to use TCM than those without TCM medication (aOR = 1.83, 1.87, and 1.79, respectively). The most commonly used formula and single CHP were Dang-Gui-Sha-Yao-San (17.25%) and Semen Cuscutae (27.40%), respectively. CHP formula combinations (e.g., Dang-Gui-Sha-Yao-San plus Wen-Jing-Tang 3.10%) or single Chinese herbal combinations (e.g., Semen Cuscutae plus Leonurus japonicus 6.31%) were also commonly used to treat female infertility. Further well-conducted, double-blind, randomized, placebo-controlled studies will be needed to evaluate the efficacy and safety of these CHP combinations for female infertility.

INTRODUCTION

Female infertility has been defined as “a paradoxical phenomenon of power between the biological and psychosexual self.” Female fertility has been defined as “the inability of a woman within childbearing age to conceive despite having frequent, unprotected intercourse for at least 1 year.” Infertility affects about 10% to 20% of couples trying to achieve pregnancy in many industrialized countries. There is an increasing number of couples seeking medical treatment. The prevalence of 1-year and 2-year infertility among newly married couples is 12.5% and 6.6%, respectively, in China. Female fertility decreases gradually with age, and more rapidly so after the age of 37. A previous study has estimated that more than 186 million ever-married women of reproductive age in developing countries are infertile. Some researchers have identified infertility as an under-observed, yet significant public health issue with profound social, psychological, and economic consequences.

The main causes of female infertility are ovulatory disorders, endometriosis, pelvic adhesion, tubal blockage and other tubal abnormalities, hyperprolactinemia, and congenital (septate uterus) and (myomas and synchiae) uterine abnormalities. Conventional therapies for female infertility include clomiphene citrate, human menopausal gonadotropin, follicle-stimulating hormone, and gonadotropin-releasing hormone analogs, aromatase inhibitor, and metformin. However, some fertility drugs increase the risk of cancer or have no pharmacological effect in infertile women aged 40 years or older. Complementary or alternative therapies such as traditional Chinese medicine (TCM) may be indicated in such cases.

Along with Western medicine, TCM is the most common form of medicine used in Taiwan. Chinese products and herbs are the most popular components of TCM. Approximately 30% of all patients use TCM in Taiwan, and about 90% of TCM users receive Chinese herbal products (CHPs) as treatment for various
A previous meta-analysis has reported that Chinese herbal medicine combined with clomiphene citrate significantly increases the pregnancy and ovulation rates, improves the cervical mucus score, and reduces the miscarriage rate compared with clomiphene citrate alone. However, large-scale, extensive studies of the most commonly used Chinese products and herbs for female infertility are lacking.

Infertility diagnoses and treatments, including those of traditional Chinese and Western medicines, are reimbursed by the National Health Insurance (NHI) in Taiwan. All medication is prescribed electronically, and the information is stored in a computer database by the National Health Research Institute (NHRI) to form the National Health Insurance Research Database (NHIRD). Due to the high coverage by the NHI, which included up to 98.3% of the population by the end of 2006 and counting, nearly all CHPs prescribed for female infertility are included in the NHIRD, making it feasible to conduct a nationwide analysis on the management of female infertility using this database.

The aim of this study was to identify the CHPs most commonly used for female infertility by analyzing a nationwide database in Taiwan. The results of this study can be used as a practical reference for further clinical trials or pharmacological experiments.

METHODS

Data Source

Taiwan’s NHI is a governmental nationwide initiative launched in 1995. The system is compulsory for Taiwanese citizens, making the coverage rate very high (it was nearly 98% of 23 million Taiwanese citizens in 1998). The government of Taiwan appointed the NHRI to lead and manage a project that would establish a database of all NHI claims. The database was named NHIRD.

This study used the Longitudinal Health Insurance Database (LHID), which is a subset of NHIRD. The LHID randomly selected 1 million insured people from 1996 to 2000. The database includes the registry for beneficiaries, the diagnosis records (based on the International Classification of Diseases, 9th Revision, Clinical Modification [ICD-9-CM]), drug prescriptions, and other medical services; the data were updated every year until 2011. LHID and NHIRD are similar in terms of age and sex distribution. The NHRI encoded the patients’ personal information for privacy protection and provided researchers with anonymous identification numbers prior to research. This study was approved by the Institutional Review Board of China Medical University in central Taiwan (CMUREC-101-012).

Study Population

We selected the study subjects from LHID. Figure 2 shows the flowchart of study population selection. Of the initial 1 million individuals, we excluded 47 subjects because of missing data on age and sex. Next, we restricted the population to the cases of female infertility (ICD-9-CM 606 and 628) in the LHID (n = 13,456). After exclusion of prevalent cases of female infertility before the end of 1999 (n = 4683) and subjects aged >55 years (n = 7), we finally included 8766 new-onset female infertility patients in our study population. TCM user was defined as an individual who resorted to TCM treatment at least once before the end of the LHID recruitment period. TCM nonuser was defined as an individual who had never received TCM treatment.

We selected some demographic factors and comorbidities to determine the potential risk factors associated with TCM usage in infertile women. The comorbidities were defined from inpatient and outpatient diagnoses made prior to the diagnosis of infertility. The comorbidities included polycystic ovary syndrome (ICD-9-CM 256.4), endometriosis (ICD-9-CM 617), uterine fibroids (ICD-9-CM 218), and irregular menstrual cycle (ICD-9-CM 626.4). We also collected data on herbal formulas and single herbal products prescribed by TCM doctors to infertile women.
Statistical Analysis

For studying the outcomes of CHPs for female infertility, descriptive statistical data of TCM users and nonusers are presented as the mean and standard deviation (SD) for age, and as the number and percentage for age group and comorbidities. To determine the association between TCM usage and potential risk factors, the odds ratio (OR) and 95% confidence interval (CI) were estimated by multivariable logistic regression. Adjusted OR would be mutually adjusted for potential source of bias. We also present the frequency and percentage of top 10 CHPs. A significance level of \( \alpha = 0.05 \) was used. Data management and analysis were performed by using SAS 9.4 software (SAS Institute Inc, Cary, NC).

RESULTS

Of the 8766 female infertility patients, 8430 were TCM users and 336 were TCM nonusers (Table 1). There were no differences in the distribution of age and polycystic ovary syndrome between TCM users and nonusers. The women with endometriosis, uterine fibroids, or irregular menstrual cycle were more likely to use TCM than those without TCM medication (aOR = 1.83, 1.87, and 1.79, respectively).

Figure 3 shows the distribution of the number of CHPs per prescription. Ninety-eight percent of all prescriptions for female infertility contained at least 2 CHPs per prescription. There was an average of 5.81 Chinese herbs in a single prescription.

| Characteristics                        | No. of cases | TCM Nonusers (%) | TCM Users (%) | Crude OR (95% CI) | Adjusted OR (95% CI) |
|----------------------------------------|--------------|------------------|---------------|-------------------|----------------------|
| Age, yr                                |              |                  |               |                   |                      |
| <27                                    | 336          | 322 (95.8)       | 7772 (92.2)   | 1.00              | 1.00                 |
| 27–29                                  | 2040 (24.7)  | 14 (4.2)         | 658 (7.8)     | 1.95 (1.13–3.35)  | 1.66 (0.96–2.87)     |
| 30–32                                  | 1943 (23.0)  | 16 (4.8)         | 764 (9.1)     | 1.99 (1.20–3.31)  | 1.83 (1.10–3.06)     |
| ≥32                                    | 2386 (28.3)  | 12 (3.6)         | 561 (6.7)     | 1.93 (1.08–3.45)  | 1.87 (1.03–3.38)     |
| Risk factors                           |              |                  |               |                   |                      |
| Polycystic ovary syndrome              |              |                  |               |                   |                      |
| No                                     | 322 (95.8)   | 14 (4.2)         | 658 (7.8)     | 1.95 (1.13–3.35)  | 1.66 (0.96–2.87)     |
| Yes                                    | 7772 (92.2)  | 7666 (90.9)      | 1.00          | 1.00              |                      |
| Endometriosis                          |              |                  |               |                   |                      |
| No                                     | 320 (95.2)   | 16 (4.8)         | 764 (9.1)     | 1.99 (1.20–3.31)  | 1.83 (1.10–3.06)     |
| Yes                                    | 7666 (90.9)  | 764 (9.1)        | 1.00          | 1.00              |                      |
| Uterine fibroids                       |              |                  |               |                   |                      |
| No                                     | 324 (96.4)   | 12 (3.6)         | 561 (6.7)     | 1.93 (1.08–3.45)  | 1.87 (1.03–3.38)     |
| Yes                                    | 7869 (93.3)  | 561 (6.7)        | 1.00          | 1.00              |                      |
| Irregular menstrual cycle              |              |                  |               |                   |                      |
| No                                     | 204 (60.7)   | 12 (3.6)         | 561 (6.7)     | 1.93 (1.08–3.45)  | 1.87 (1.03–3.38)     |
| Yes                                    | 3834 (45.5)  | 7869 (93.3)      | 1.00          | 1.00              |                      |

Table 4 shows the top 5 most used combinations of CHP pairs. Dang-Gui-Sha-Yao-San plus Wen-Jing-Tang was the most commonly prescribed 2-formula combination (3.1%), Fructus ligustri lucidi plus Eclipta prostrata L. was the most commonly prescribed 2-single CHP combination (6.3%).

**DISCUSSION**

This is an important large-scale survey of Chinese herbal prescriptions and herbs used in the treatment of female infertility in a Taiwanese population. We found that, in addition to visiting the gynecologist, the majority of these patients (96.17%) also sought TCM treatment. It seemed high demand for infertile women with traditional Chinese medicine treatment as a complementary or alternative medicine. We explored the correlation of use of TCM treatment, and noted that female infertility patients with infertility risk factors such as endometriosis, uterine fibroids, or irregular menstrual cycle were more likely to use TCM than those without TCM medication. Endometriosis, uterine fibroids, or irregular menstrual cycle may affect infertility. Our study has shown that the more comorbidities per disease, the more likely are individuals to seek treatment—either traditional Chinese or Western medicine treatment.

We found that the most common individual Chinese herbal prescriptions and herbs among female infertility patients were Dang-Gui-Sha-Yao-San and Semen Cuscutae. Dang-Gui-Sha-Yao-San is a herbal mixture used for abdominal pain during pregnancy. Previous reports revealed that Dang-Gui-Sha-Yao-San corrects luteal phase insufficiency via an antioxidant mechanism or an antagonistic action on both prostaglandin L. japonicus (13.55%), Fructus ligustri lucidi (13.43), Cypers rotundus L. (12.13%), and Dipsacus asper Wall (11.71%).
F2-α and acetylcholine-induced uterine contraction.\(^{33}\) *Semen Cuscutae* improves ovarian endocrine dysfunction and increases estrogen receptor expression in the hippocampus, hypothalamus, and pituitary glands, as well as luteinizing hormone receptor expression in the ovaries.\(^{34}\) One other study reported that *Semen Cuscutae* regulates the proliferation and apoptosis of the decidua and cytotrophoblasts, thus preventing spontaneous abortions.\(^{35}\) In Taiwan, Dang-Gui-Sha-Yao-San and *Semen Cuscutae* often used synergistically to optimize the treatment for female infertility through individualized therapy. Another herbal formula, Wen-Jing-Tang, improves the endocrine condition in the treatment of disturbances of ovulation\(^{36}\) and suppresses the contraction of uterus smooth muscle.\(^{37}\) *Leonurus japonicus* was reported to have an antioxidative effect on the uterus.\(^{38}\)

In addition, we also noted that combinations of CHPs such as Dang-Gui-Sha-Yao-San plus Wen-Jing-Tang or single herbal combinations such as *Semen Cuscutae* plus *Leonurus japonicus* were commonly used to treat female infertility. Mixed formulations are usually prescribed in combination to enhance efficacy, minimize toxicity, or tailor the treatment according to individual needs. Our results also showed that on average, 5.81 types of CHPs are prescribed per prescription. These results should be taken into account by physicians when devising individualized therapy for female infertility.

Since the NHIRD is a very complete database including 22.60 million of 22.96 million people, the representativeness of this database is reliable and strong to provide some information of the patients’ medical seeking behavior and physicians’ prescription patterns in Taiwan. The completeness of NHIRD and nationwide population-based study design increase the validity of the study results. However, 1 limitation of our study was that we did not determine the efficacy of therapeutic effects. We found the most commonly used CHPs, but not necessarily the most effective ones. Although the NHIRD contains large amounts of prescription data, chart-level records (i.e., physician notes, laboratory reports, and imaging studies) are not available. Thus, it was not possible to evaluate the

### TABLE 2. Top 10 Chinese Herbal Product Formulas Prescribed by Traditional Chinese Medicine Doctors to Female Infertility Patients From 2000 to 2011 in Taiwan (Total Number of Prescriptions, \(n = 18,860\))

| CHP Formulas                  | Ingredients                                                                                           | Number (%)    |
|-------------------------------|--------------------------------------------------------------------------------------------------------|---------------|
| Dang-Gui-Sha-Yao-San          | *Angelicae sinensis* Radix; *Paeoniae Radix*; *Asian*; *Atractylodis ovatae Rhizoma*; *Alismatis Rhizoma*; *Ligustici Rhizoma* | 3253 (17.25)  |
| Wen-Jing-Tang                 | Cinnamomi Ramulus; *Evodiae Fructus*; *Ligustici Rhizoma*; *Angelicae sinensis* Radix; *Paeoniae Radix*; *Zingiberis Rhizoma Recens*; Moutan Radicis Cortex; *Ophiopogonis Tuber*; *Pinelliae Tuber*; *Ginseng Radix*; *Glycyrrhizae Radix*; Asini Corii Gelatinum | 3086 (16.36)  |
| Jia-Wei-Xiao-Yao-San          | *Moutan Radicis Cortex*; *Radix Paeoniae Rubra*; Bupleuri Radix; *Angelicae Sinensis* Radix; *Atractylodis Ovatae Rhizoma*; *Poria*; *Glycyrrhizae Radix*; *Zingiberis Rhizoma Recens*; *Menthae Herba* | 2800 (14.85)  |
| You-Gui-Wan                  | Rhizoma Rehmanniae Praeparata; *Rhizoma Dioscoreae*; *Fructus Lycii*; *Fructus Corni*; *Radix Cyathulae*; *Semen Cuscutae*; *Colla Cornus Cervi*; *Colla Piastr Testudinis* | 2747 (14.57)  |
| Zou-Gui-Wan                   | Rhizoma Rehmanniae Praeparata; *Rhizoma Dioscoreae*; *Fructus Lycii*; *Semen Cuscutae*; *Colla Cornus Cervi*; *Fructus Corni*; *Angelicae sinensis Radix*; *Radix Aconiti Praeparata*; *Cinnamomum cassia Blume*; *Eucommia ulmoides Oliv.* | 1880 (9.97)   |
| Shen-Ling-Bai-Zhu-San         | Ginseng Radix; *Atractylodis Ovatae Rhizoma*; *Poria*; *Glycyrrhizae Radix*; *Dioscoreae Rhizoma*; *Lablab Semen*; *Nelumbinis Semen*; *Platyodonis Radix*; *Coicis Semen*; *Amomi Semen* | 1754 (9.30)   |
| Gui-Zhi-Fu-Ling-Wan           | Cinnamomi Ramulus; *Poria*; *Moutan Radicis*; *Persicae Semen*; *Paeoniae Radix* | 1314 (6.97)   |
| Si-Wu-Tang                    | *Angelicae sinensis* Radix; *Rehmanniae Radix*; *Paeoniae Radix*; *Ligustici Rhizoma*               | 1205 (6.39)   |
| Shao-Fu-Zhu-Yu-Tang           | *Fructus Foenicui*; *Rhizoma Zingiberis*; *Rhizoma Corydalis*; *Angelicae sinensis Radix*; *Rhizoma Ligustici Chuanxizong*; *Cortex Cinnamomi*; *Radix Paeoniae Rubra*; *Pollen Typhae*; *Faeces Trogopterorum* | 950 (5.04)    |
| Gui-Pi-Tang                   | *Atractylodis Ovatae Rhizoma*; *Poria*; *Astragali Radix*; *Ginseng Radix*; *Glycyrrhizae Radix*; *Saussureae Radix*; *Angelicae sinensis Radix*; *Polygalae Radix*; *Longanae Arillus*; *Zizyphi Spinosi Semen* | 911 (4.83)    |

CHP = Chinese herb product, TCM = traditional Chinese medicine.
effectiveness of the treatments. The other one was that the database did not contain some potential confounders such as education, smoking, alcohol consumption, and economic state, which may also be associated with female infertility.

In conclusion, CHPs are commonly used for the treatment of female infertility in Taiwan. Various CHPs with particular effects are used synergistically to optimize the treatment of female infertility. Data mining analysis helped identify the most commonly prescribed CHP combinations. Dang-Gui-Sha-Yao-San and Jia-Wei-Xiao-Yao-San were the most frequently prescribed CHPs by TCM doctors in Taiwan for female infertility. These results provide information for individualized therapy of female infertility.

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