Introduction

Infertility is an integral part of reproductive health and a priority global health issue. This condition is also a critical problem that has to be solved by many countries with low birth rates. In 2010, approximately 48.5 million infertile couples worldwide cannot have a child after five years of trying to procreate, with the highest prevalence of infertility in South Asia, North Africa/Middle East, Sub-Saharan Africa, Central Asia, and Central/Eastern Europe [1]. Procreation is one of the natural needs of human beings, and infertility is one of the important factors associated with the quality of life for married couples. Married couples may experience emotional problems because of pregnancy failure and may face the risk of social dysfunction, anxiety, and depression [2].

Taiwan has a very low birth rate, resulting from the current aging society. Taiwan is one of the countries with the lowest fertility rates globally. One cause of low birth rate is the increasing prevalence of infertility since 1990. The female total fertility rate fell from 7.04 in 1951 to 1.13 in 2017 in Taiwan [3]. Female infertility is defined as inability of a...
woman within childbearing age to conceive despite having frequent, unprotected intercourse for at least 1 year [4]. The inability to have children can result in psychological distress and emotional problem. Seeking alternative treatments for infertility is one solution to this public health problem.

Many causes of female infertility are menstrual abnormalities, endometriosis, pelvic adhesion, ovulatory disorders, tubal blockage, hyperprolactinemia, and uterine abnormalities [5, 6]. Western medicine therapies for female infertility include clomiphene citrate, gonadotropin-releasing hormone analogs, follicle-stimulating hormone, metformin, and aromatase inhibitor [7, 8]. Some fertility drugs have no significant effect in fertile women aged 40 years or older, while some drugs increase the risk of cancer. Traditional Chinese medicine (TCM) is commonly used for complementary or alternative therapies in these cases in Asian countries.

In addition to biomedicine, TCM is the most common form of medicine used in Taiwan. Two meta-analysis pooling randomized controlled trials (RCTs) have reported that clomiphene citrate combined with TCM significantly increased the pregnancy and ovulation rates, increased the cervical mucus score, and reduced the miscarriage rate compared with clomiphene citrate alone [9, 10]. A cross-sectional study of 8,766 new onset cases of female infertility reported the prevalence and associated factors of TCM use, as well as the top 10 Chinese herbal product (CHP) formulas for female infertility [11]. However, these studies did not explore the specific effect of TCM treatment on infertile outcomes. Thus, the present study was aimed to examine the association between TCM treatment with successful pregnancy among infertile women using population-based case-control study with matching approach to reduce the confounding effects through assembling a sample in which potential confounding factors are balanced between TCM and non-TCM groups.

2. Methods

2.1. Data Sources. The Taiwan National Health Insurance (NHI) program is a compulsory and nationwide single-payer insurance program that began in 1995. It covers almost the entire population (99.6%) of Taiwan. The Bureau of NHI has an expert review of random samples of every 50–100 outpatient and inpatient claims from each hospital and clinic in Taiwan every three months, and false reports of diagnoses have severe penalty [12]. The National Health Insurance Research Database (NHIRD) contains the following information: demographic data; dates of clinical visits; details of prescriptions and expenditure amounts of beneficiaries; diagnostic codes by the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM). Data also included detailed diagnoses and treatments provided by TCM physicians.

This study used the Longitudinal Health Insurance Database 2000 (LHD2000) of NHIRD. The LHD2000 of NHIRD sample and the entire population of NHIRD are similar in terms of age and sex distributions. The LHD2000 of NHIRD contains all outpatient and inpatient claim data of one million beneficiaries who were randomly sampled for 23 million enrollees in the NHI.

The case-control study was conducted using the registration and claim datasets for 2000–2011 from the LHD2000 of NHIRD. The female infertility in the dataset was that covered by the NHI Program. The NHI program has a committee that reviews new treatments (containing biomedicine and TCM), drugs, and procedure, and those that have evidence for their efficacy are covered. The present study was approved by the Institutional Review Board of the Public Health, Social, and Behavioral Science Committee Research Ethics Committee, China Medical University and Hospital (CMU-REC-101-012). Informed consent of the study participants was not required because the dataset used in this study consists of deidentified secondary data released for research purposes.

2.2. Study Subjects. A population-based case-control study was conducted using registration and claim datasets of the NHIRD for 2000–2011. The population-based case-control study can minimize the selection bias because cases are generally representative of the population of women with successful pregnancy and the controls are a representative sample, too. Infertile women were considered if a diagnostic code (ICD-9-CM code: 628) was found during 2000–2010 of the LHD2000 of NHIRD with at least three ambulatory claims. In the clinical practice of Taiwan, the diagnosis of infertility involves the evaluation of a couple. Diagnosis of infertility for a women is as inability of a couple to conceive after 12 months of regular, unprotected intercourse in women less than 35 years of age and after six months of regular intercourse without use of contraception in women 35 years and older or who have one of the following in their medical history or physical examination: history of irregular menstrual cycles over 35 days apart or no periods at all and known or suspected problems with the uterus, tubes, or other problems in the abdominal cavity such as endometriosis or adhesions [13]. For an evaluation, a couple must attend clinic simultaneously but take medical history separately to detect the most common causes of infertility, including menstrual history, assessment of luteinizing hormone surge in urine before ovulation, and/or luteal phase progesterone level to assess ovulatory function. Then, the assessment of tubal patency and the uterine cavity is performed through hysterosalpingogram or sonohysterogram with a test of tubal patency such as hysterosalpingocontrast-sonography to detect abnormalities in the uterine cavity. This test also assesses whether the fluid passes out of the uterus and spills out of the fallopian tubes and sometimes the test itself can improve fertility for some women by flushing out and opening the fallopian tubes. If abnormal tests are found, further evaluation is needed. The other common assessments included ovarian reserve with day 3 serum follicle-stimulating hormone for determination of the quality and quantity of eggs available for ovulation, estradiol levels, anti-Müllerian hormone, antral follicle count, and/or thyroid-stimulating hormone that control reproductive processes. Some imaging tests may be needed.
such as pelvic ultrasound, looking for uterine or fallopian tube disease, and sonohysterogram, seeing details inside the uterus that cannot be seen on a regular ultrasound. For some rare cases, other imaging tests may be needed, including a hysteroscopy to look for uterine or fallopian tube disease, a laparoscopy to examine the fallopian tubes, ovaries and uterus, and a genetic testing to look for a genetic defect.

A total of 7,765 infertile women were identified. After excluding 467 women without information of age at onset, insured amount, and residential area, 7,298 women were found to be eligible. Among these eligible women, 2,627 were found to have successful pregnancies and were included as the case group. After frequency-matching with birth year, 2,627 women without pregnancy were included as the control group (Figure 1).

To calculate the exposure period for TCM use, we used the following algorithm. For women with successful pregnancy, the assumed fertility date (day zero) was defined as follows: delivery date minus 270 days if no preterm birth was identified using ICD-9-CM code; delivery date minus 245 days if a preterm birth of unspecified gestational age was identified using ICD-9-CM code; and delivery date minus the upper boundary of the gestational age range in case of an indication for preterm birth by ICD-9-CM code with a specified range. For example, for an ICD-9-CM code 765.26, i.e., 31 to 32 weeks of gestation, the date of delivery minus 224 days for deliveries. The exposure period for TCM use was then defined as one year before the assumed fertility date. For those without successful pregnancy, their assumed fertility dates were assigned using their matched cases. In addition, the treatments for Western medicine with the same exposure period for TCM use were considered, including clomiphene citrate/tamoxifen, gonadotropin-releasing hormone (GnRH) agonist/GnRH antagonist, progesterone, and bromocriptine/cabergoline. To protect the patients’ privacy, the NHIRD cryptographically scrambled data on their identities and institutions in the NHIRD.

2.3. Statistical Analysis. Continuous variables were reported as mean and standard deviation, while categorical variables were reported as number and percentage. The chi-square and t-test were used to compare differences in the baseline differences between two groups for successful pregnancy status. A univariate logistic analysis was then conducted to examine the magnitude of the associations between female infertility and TCM use as well as comorbidities. Adjusted odds ratios (ORs) and their 95% confidence intervals (CIs) were then estimated by multivariate logistic regression analysis. Stratified analyses were performed according to common gynecologic disorders (including polycystic ovary syndrome, endometriosis, irregular menstrual cycle, uterine fibroids, and dysmenorrhea), and interactions between TCM use and these gynecologic disorders were examined by their product term. In addition, we performed a sensitivity analysis to rule out the potential confounding effect of Western medicine use by excluding women with Western fertility drug use. The statistical significance was set to two-sided \( p < 0.05 \). All analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC, USA).

3. Results

Baseline sociodemographic factors and comorbidities were presented according to the pregnancy status (women with pregnancy as cases and without pregnancy as controls) in Table 1. As age increased, the likelihood of successful pregnancy decreased (for 30–39 years: OR = 0.68, 95% CI = 0.60–0.76; and for ≥40 years: OR = 0.22, 0.13–0.37) (Table 2). Compared with those without TCM use during one year before assumed fertility date, TCM users were significantly associated with successful pregnancy (OR = 1.50, 1.35–1.68) without considering the other covariates. After adjustment, the results remain similar (OR = 1.48, 1.31–1.66). If we excluded women with any Western medicine use to rule out the confounding effect of Western medicine use, the multivariate-adjusted OR for TCM use was 1.60 (1.39, 1.83), which is similar to the adjusted OR for the entire sample (S2 Table). After further considering the frequency of outpatient visits, TCM users with 1–3 and >3 outpatient visits were associated with 22% and 73% increased odds of successful pregnancy, respectively, after multivariate adjustment (OR = 1.22, 1.05–1.41 and OR = 1.73, 1.50–1.98). Considering the number of days for drug prescription, TCM users with 1–14 and >14 days for drug prescription were associated with 25% and 73% increased odds of successful pregnancy, respectively, after multivariate adjustment (OR = 1.25, 1.07–1.47 and OR = 1.73, 1.51–1.97). The other significant factors after adjustment were insured amount (OR = 1.33, 1.10–1.62 for 40,000–59,9999 NT$/month; OR = 1.76, 1.35–2.30 for ≥60,000 NT$/month); insured unit (OR = 0.77, 0.63–0.94 for private enterprise employees; OR = 0.75, 0.58–0.98 for member of occupational sector; OR = 0.69, 0.49–0.98 for farmers and fishermen; OR = 0.59, 0.44–0.78 for low-income households, veterans, and other regional), comorbidity of diabetes (OR = 0.94, 0.22–0.84) and dysmenorrhea (OR = 0.75, 0.61–0.93), and fertility drugs of clomiphene citrate/tamoxifen (OR = 3.53, 3.06–4.08), progesterone (OR = 2.53, 1.89–3.38), and bromocriptine/cabergoline (OR = 2.20, 1.48–3.27). The distribution of combination for Western medicine and TCM used and the ORs of successful pregnancy are presented in S1 Table. Compared with those without both TCM and Western medicine use during one year before assumed fertility date, Western medicine use only, TCM use only, and both Western medicine and TCM use were significantly associated with successful pregnancy (OR: 5.20, 4.27–6.35; 1.61, 1.41–1.84; and 5.89, 4.91–7.07, respectively) without considering the other covariates. After adjustment, the results remain similar (OR = 4.96, 4.05–6.07; 1.60, 1.40–1.83; and 5.75, 4.77–6.93, respectively). Both TCM and Western medicine use significantly increase the odds of successful pregnancy over the use of just Western medicine alone (p for interaction of TCM use and Western medicine use = 0.02).

Table 3 shows that Jia-Wei-Xiao-Yao-San was the most commonly prescribed herbal formula (n = 253, 4.82%), followed by Wen-Jing-Tang (n = 213, 4.05%), Dang-Gui-Sha-Yao-San (n = 207, 3.94%), Zou-Gui-Wan (n = 152, 2.89%), Gui-Zhi-Fu-Ling-Wan (n = 127, 2.42%),
and You-Gui-Wan (n = 115, 2.19%). Table 4 shows that the effects of the top 10 TCM formulas were all significant. Jia-Wei-Xiao-Yao-San, Dang-Gui-Sha-Yao-San, Gui-Zhi-Fu-Ling-Wan, and Si-Wu-Tang had significant adjusted OR greater than 3 (the corresponding ORs and 95% CIs were as follows: 3.17, 2.35–4.28; 3.14, 2.26–4.37; 3.27, 2.13–5.02; and 4.25, 2.18–8.30), and Wen-Jing-Tang, Zou-Gui-Wan, You-Gui-Wan, Shao-Fu-Zhu-Yu-Tang, and Liu-Wei-Dihuang-Wan had significant adjusted OR greater than 2 (the corresponding ORs and 95% CIs were as follows: 2.83, 2.06–3.90; 2.47, 1.71–3.56; 2.12, 1.41–3.18; 2.54, 1.67–3.86; and 2.52, 1.51–4.21). And fertility drugs of clomiphene citrate/tamoxifen, progesterone, and bromocriptine/cabergoline remained significant (OR = 3.76, 3.26–4.34; 3.22, 2.44–4.26; 2.94, 2.00–4.32, respectively). To rule out the confounding effects of Western medicine use by excluding infertility women with any Western medicine use, the values of ORs for individual commonly used fertility drugs became larger and remain statistically significant after multivariate adjustment (S3 Table).

Figure 2 shows that the OR and 95% CI were significant without comorbidities for the above syndrome (the ORs and 95% CIs for no polycystic ovary syndrome, endometriosis, irregular menstrual cycle, uterine fibroids, and dysmenorrhea were as follows: 1.48, 1.31–1.67; 1.47, 1.31–1.66; 1.39, 1.21–1.60; 1.52, 1.35–1.71; and 1.48, 1.31–1.68). In addition, the effect of TCM on successful pregnancy for irregular menstrual cycle (OR = 1.71, 1.39–2.12) remained significant. No significant interaction between TCM use and the above syndromes was observed.

4. Discussion

This large-scale case-control study of TCM use in the treatment of female infertility consisted of 2,627 infertile women with successful pregnancy and 2,627 frequency-matched infertile women without successful pregnancy in a Taiwanese population. The results demonstrated an overall 48% increase in successful pregnancy for women receiving TCM compared with those not receiving TCM. The infertile women with diabetes and endometriosis were associated with decreased likelihood for successful pregnancy. The top four prescriptions with the strongest strength of association with successful pregnancy were Si-Wu-Tang, Gui-Zhi-Fu-Ling-Wan, Jia-Wei-Xiao-Yao-San, and Dang-Gui-Sha-Yao-San with corresponding ORs of 4.25, 3.27, 3.17, and 3.14. Subgroup analysis revealed that the magnitude of association between TCM use and successful pregnancy in women with endometriosis and irregular menstrual cycle was slightly higher.

The 10 most common TCM prescriptions used by female infertility in this study were similar to those reported by Lin et al. who explored the TCM use for dysfunctional uterine bleeding [11] in 7 common prescriptions. This study was also consisted with that of Hung et al. who investigated the TCM use for female infertility with 10 common prescriptions [14]. However, the strength of association between outcomes and TCM prescription and subgroup analysis based on the status of gynecological diseases were not examined in these two studies. We found that Jia-Wei-Xiao-Yao-San, Wei-Jing-Tang, Dang-Gui-Sha-Yao-San, and Gui-Zhi-Fu-Ling-Wan exhibited the strongest effect on improving female fertility. Jia-Wei-Xiao-Yao-San was also reported to be the most common prescription used in treating patients with colon or breast cancer [15–17] and dysfunctional uterine bleeding [11].

This study is the first large-scale case-control to report the association between successful pregnancy and TCM used in infertile women in Taiwanese society. Our sample is representative of the general population. Given the high coverage rate of NHI on TCM healthcare, the TCM prescription data are completely recorded in the NHI databases. Thus, the likelihood of potential recall or differential measurement bias was minimized. The TCM prescription...
### Table 1: Infertility patient characteristics with or without pregnancy.

| Characteristic                        | Infertility women (n = 5,254) | p value |
|---------------------------------------|-------------------------------|---------|
|                                       | No successful pregnancy (n = 2,627) | Successful pregnancy (n = 2,627) |
| **Birth year**                        |                               |         |
| 1959–1969                             | 518 (19.72)                   | 518 (19.72) | 1.00     |
| 1970–1979                             | 1699 (64.67)                  | 1699 (64.67) |
| 1980–1988                             | 410 (15.61)                   | 410 (15.61) |
| **Age at diagnosis**                  |                               | <0.001  |
| 20–29                                 | 1166 (44.39)                  | 1427 (54.32) |
| 30–39                                 | 1376 (52.38)                  | 1181 (44.96) |
| ≥40                                   | 85 (3.24)                     | 19 (0.72)  |
| **One-year period before assumed fertility date** |                               | <0.001  |
| TCM nonusers                          | 1348 (51.31)                  | 1083 (41.23) |
| TCM users                             | 1279 (48.69)                  | 1544 (58.77) |
| Number of outpatient visits†          | 6.64 ± 7.78                   | 7.62 ± 8.24  |
| Days of administration†               | 36.08 ± 47.05                 | 46.47 ± 56.34 |
| **Insured amount (NT$/month)**        |                               | <0.001  |
| <20,000                               | 1066 (40.58)                  | 935 (35.59)  |
| 20,000–39,999                         | 1032 (39.28)                  | 1008 (38.37) |
| 40,000–59,999                         | 388 (14.77)                   | 488 (18.58)  |
| ≥60,000                               | 141 (5.37)                    | 196 (7.46)   |
| **Urban level**                       |                               | 0.09     |
| 1                                     | 910 (34.64)                   | 946 (36.01)  |
| 2                                     | 861 (32.78)                   | 796 (30.3)   |
| 3                                     | 409 (15.57)                   | 458 (17.43)  |
| ≥4                                    | 447 (17.02)                   | 427 (16.25)  |
| **Residential area**                  |                               | 0.88     |
| Northern                              | 401 (15.26)                   | 399 (15.19)  |
| Taipei                                | 995 (37.88)                   | 1032 (39.28) |
| Central                               | 459 (17.47)                   | 436 (16.6)   |
| Southern                              | 333 (12.68)                   | 337 (12.83)  |
| Eastern                               | 39 (1.48)                     | 41 (1.56)    |
| Kao-Ping                              | 400 (15.23)                   | 382 (14.54)  |
| **Insured unit**                      |                               | <0.001  |
| Government, school employees           | 248 (9.44)                    | 357 (13.59)  |
| Private enterprise employees           | 1597 (60.79)                  | 1661 (63.23) |
| Member of occupational                | 324 (12.33)                   | 270 (10.28)  |
| Farmers, fishermen                     | 139 (5.29)                    | 114 (4.34)   |
| Low-income households veterans, other regions | 319 (12.14)                | 225 (8.56)   |
| **Comorbidities**                     |                               |         |
| Hypertension                          | 27 (1.03)                     | 13 (0.49)   | 0.04     |
| Diabetes                              | 40 (1.52)                     | 14 (0.53)   | <0.001  |
| Hypercholesterolemia                  | 32 (1.22)                     | 19 (0.72)   | 0.09     |
| Obesity                               | 20 (0.76)                     | 10 (0.38)   | 0.10     |
| Cerebral vascular disease             | 8 (0.30)                      | 6 (0.23)    | 0.79     |
| COPD                                  | 143 (5.44)                    | 138 (5.25)  | 0.81     |
| Renal failure                         | 6 (0.23)                      | 3 (0.11)    | 0.50     |
| Tobacco use                           | 2 (0.08)                      | 1 (0.04)    | 1.00     |
| Anemia                                | 22 (0.84)                     | 17 (0.65)   | 0.52     |
| Polycystic ovary syndrome             | 104 (3.96)                    | 104 (3.96)  | 1.00     |
| Endometriosis                         | 181 (6.89)                    | 133 (5.06)  | 0.006    |
| Irregular menstrual cycle             | 883 (33.61)                   | 862 (32.81) | 0.56     |
| Uterine fibroids                      | 127 (4.83)                    | 84 (3.20)   | 0.003    |
| Dysmenorrhea                          | 253 (9.63)                    | 203 (7.73)  | 0.01     |
| **Fertility drugs**                   |                               |         |
| Clomiphene citrate/tamoxifen          | 340 (12.94)                   | 959 (36.51) | <0.001  |
| GnRH agonist/GnRH antagonist           | 0 (0.00)                      | 2 (100.00)  | 0.50     |
| Progesterone                          | 70 (2.66)                     | 220 (8.37)  | <0.001  |
| Bromocriptine/cabergoline             | 3 (1.41)                      | 110 (4.19)  | <0.001  |

TCM: traditional Chinese medicine; CAD: coronary artery diseases; COPD: chronic obstructive pulmonary disease. p values for chi-square or Fisher’s exact test; †: mean ± standard deviation for TCM users.
Table 2: Unadjusted and adjusted odd ratios and 95% confidence interval of successful pregnancy among women with infertility.

| Characteristic                                    | Unadjusted OR (95% CI) | Adjusted OR (95% CI) |
|--------------------------------------------------|------------------------|----------------------|
| Age at diagnosis                                 |                        |                      |
| 20–29                                            | 1.00                   | 1.00                 |
| 30–39                                            | 0.70 (0.63, 0.78)***    | 0.68 (0.60, 0.76)***  |
| ≥40                                              | 0.18 (0.11, 0.30)***    | 0.22 (0.13, 0.37)***  |
| One-year period before assumed fertility date     |                        |                      |
| TCM nonusers                                     | 1.00                   | 1.00                 |
| TCM users                                        | 1.50 (1.35, 1.68)***    | 1.48 (1.31, 1.66)***  |
| Number of outpatient visits                      |                        |                      |
| 0                                                | 1.00                   | 1.00†                |
| 1–3                                              | 1.25 (1.09, 1.43)***    | 1.22 (1.05, 1.41)***  |
| >3                                               | 1.74 (1.53, 1.98)***    | 1.73 (1.50, 1.98)***  |
| Number of days for drug prescription             |                        |                      |
| 0                                                | 1.00                   | 1.00†                |
| 1–14                                             | 1.30 (1.12, 1.51)***    | 1.25 (1.07, 1.47)***  |
| >14                                              | 1.76 (1.55, 1.99)***    | 1.73 (1.51, 1.97)***  |
| Insured amount (NT$/month)                       |                        |                      |
| <20,000                                          | 1.00                   | 1.00                 |
| 20,000–39,999                                    | 1.11 (0.98, 1.26)       | 1.06 (0.92, 1.23)    |
| 40,000–59,999                                    | 1.43 (1.22, 1.68)***    | 1.33 (1.10, 1.62)**   |
| ≥60,000                                          | 1.59 (1.26, 2.00)***    | 1.76 (1.35, 2.30)**   |
| Urban level                                      |                        |                      |
| 1                                                | 1.00                   | 1.00                 |
| 2                                                | 0.89 (0.78, 1.02)       | 0.87 (0.74, 1.02)    |
| 3                                                | 1.08 (0.92, 1.27)       | 1.09 (0.90, 1.33)    |
| ≥4                                               | 0.92 (0.78, 1.08)       | 0.98 (0.79, 1.21)    |
| Residential area                                 |                        |                      |
| Taipei                                           | 1.00                   | 1.00                 |
| Northern                                         | 0.96 (0.81, 1.13)       | 1.02 (0.84, 1.24)    |
| Central                                          | 0.92 (0.78, 1.07)       | 0.88 (0.72, 1.07)    |
| Southern                                         | 0.98 (0.82, 1.16)       | 1.06 (0.86, 1.32)    |
| Eastern                                          | 1.01 (0.65, 1.59)       | 0.81 (0.49, 1.34)    |
| Kao-Ping                                         | 0.92 (0.78, 1.09)       | 0.99 (0.82, 1.20)    |
| Insured unit                                     |                        |                      |
| Government, school employees                     | 1.00                   | 1.00                 |
| Private enterprise employees                     | 0.72 (0.61, 0.86)***    | 0.77 (0.63, 0.94)*    |
| Member of occupational                           | 0.58 (0.46, 0.73)***    | 0.75 (0.58, 0.98)*    |
| Farmers, fishermen                               | 0.57 (0.42, 0.77)***    | 0.69 (0.49, 0.98)*    |
| Low-income households veterans, other regions    | 0.49 (0.39, 0.62)***    | 0.59 (0.44, 0.78)**   |
| Comorbidities                                    |                        |                      |
| Hypertension                                     | 0.48 (0.25, 0.93)*      | 0.84 (0.41, 1.73)    |
| Diabetes                                         | 0.35 (0.19, 0.64)***    | 0.43 (0.22, 0.84)*    |
| Hypercholesterolemia                             | 0.59 (0.33, 0.95)       | 0.90 (0.48, 1.70)    |
| Obesity                                          | 0.50 (0.23, 1.07)       | 0.71 (0.31, 1.59)    |
| Cerebral vascular disease                        | 0.75 (0.26, 2.17)       | 0.61 (0.19, 1.96)    |
| COPD                                             | 0.96 (0.76, 1.23)       | 0.93 (0.71, 1.20)    |
| Renal failure                                    | 0.50 (0.13, 2.00)       | 0.61 (0.13, 2.81)    |
| Tobacco use                                      | 0.50 (0.05, 5.52)       | 0.65 (0.06, 7.46)    |
| Anemia                                           | 0.77 (0.41, 1.46)       | 0.70 (0.36, 1.38)    |
| Polycystic ovary syndrome                        | 1.00 (0.76, 1.32)       | 0.97 (0.72, 1.32)    |
| Endometriosis                                    | 0.72 (0.57, 0.91)***    | 0.88 (0.68, 1.14)    |
| Irregular menstrual cycle                        | 0.97 (0.86, 1.08)       | 0.91 (0.81, 1.04)    |
| Uterine fibroids                                 | 0.65 (0.49, 0.86)**     | 0.86 (0.63, 1.17)    |
| Dysmenorrhea                                     | 0.79 (0.65, 0.95)*      | 0.75 (0.61, 0.93)**   |
| Fertility drugs                                  |                        |                      |
| Clomiphene citrate/tamoxifen                     | 3.87 (3.37, 4.44)***    | 3.53 (3.06, 4.08)***  |
| GnRH agonist/GnRH antagonist                     | —                      | —                    |
| Progesterone                                     | 3.34 (2.54, 4.39)***    | 2.53 (1.89, 3.38)***  |
| Bromocriptine/cabergoline                        | 3.06 (2.10, 4.46)***    | 2.20 (1.48, 3.27)***  |

OR: odd ratio; * p < 0.05; ** p < 0.01; *** p < 0.001. †: multivariate-adjusted for age at diagnosis, insured amount, urban level, residential area, insured unit, and comorbidities.
includes herbal or formulas prescribed by board-certified TCM physicians. The complete information on TCM prescription facilitates the investigation of the independent effects of each type of prescription on the pregnancy outcome in female infertility. This process is more comprehensive than merely evaluating a particular type of TCM prescription.

Our study reports the top 10 commonly prescribed formulas for female infertility. A previous epidemiological prospective cohort study noted that Jia-Wei-Xiao-Yao-San ameliorated depression in menopausal women compared with those administered antidepressants by increasing the serum TNF-α after 12 weeks of treatment [18]. In another multicenter, randomized, double-blinded, placebo-controlled study, persons treated with multicomponent extract of Jia-Wei-Xiao-Yao-San showed significantly decreased anxiety symptoms compared with those with individual extract mixture, and placebo group [19].

The findings indicated that Si-Wu-Tang was the TCM formula exerted strongest association with successful pregnancy. Si-Wu-Tang was administered for blood deficiency, which is particularly common in women because of

---

### Table 3: The TCM name, ingredients or generic name, and functional classification of the commonly used TCM prescriptions in patients with female infertility.

| TCM name              | Ingredients or generic name                                                                 | Functional classification                                                                 | No. of users (%#) | Successful pregnancy | No successful pregnancy |
|-----------------------|---------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------|------------------|----------------------|------------------------|
| Jia-Wei-Xiao-Yao-San  | Moutan Radicis Cortex; Radix Paeonae Rubra; Bupleuri Radix; Angelicae sinensis Radix; Atractylodis ovatae Rhizoma; Poria; Glycyrrhizae Radix; Zingiberis Rhizoma Recens; Menthae Herba | Shugan Jieyu, heat-clearing and nourishing blood                                           | 194 (7.38%)      | 59 (2.25%)           |
| Wen-Jing-Tang         | Cinnamomum Ramulus; Evodiae Fructus; Ligustici Rhizoma; Angelicae sinensis Radix; Paeonae Radix; Zingiberis Rhizoma Recens; Moutan Radicis Cortex; Ophiopogonis Tuber; Pinelliae Tuber; Ginseng Radix; Glycyrrhizae Radix; Asini Corii Gelatinum | Promoting blood circulation and removing blood stasis, warming meridian and removing cold, benefiting qi, and nourishing blood | 160 (6.09%)      | 53 (2.02%)           |
| Dang-Gui-Sha-Yao-San  | Angelicae sinensis Radix; Paeoniae Radix; Poria; Atractylodis ovatae Rhizoma; Alismatis Rhizoma; Ligustici Rhizoma | Nourishing blood and regulating the liver, and tonifying the spleen and dampness           | 158 (6.01%)      | 49 (1.87%)           |
| Zou-Gui-Wan           | Rhizoma Rehmanniae Preparata; Rhizoma Dioscoreae; Fructus Lycii; Fructus Corni; Radix Cyathulae; Semen Cuscutae; Colla Cornus Cervi; Colla Plastri Testudinis | Nourishing yin and tonifying the kidney, and filling essence                              | 110 (4.19%)      | 42 (1.60%)           |
| Gui-Zhi-Pu-Ling-Wan   | Cinnamomum Ramulus; Poria; Moutan Radicis; Persicae Semem; Paeoniae Radix Rubra             | Promoting blood circulation and removing blood stasis removing blocked mass                | 99 (3.77%)       | 28 (1.07%)           |
| You-Gui-Wan           | Rhizoma Rehmanniae Preparata; Rhizoma Dioscoreae; Fructus Lycii; Semen Cuscutae; Colla Cornus Cervi; Fructus Corni; Angelicae sinensis Radix; Radix Aconiti Preparata; Cinnamomum cassia Blume; Eucommia ulmoides Oliv. | Warming kidney yang, replenishing essence, and enriching the blood                         | 80 (3.05%)       | 35 (1.33%)           |
| Shao-Fu-Zhu-Yu-Tang   | Fructus Foenicuitt; Rhizoma Zingiberis; Rhizoma Corydalis; Angelicae sinensis Radix; Rhizoma Ligustici Chuanxiong; Cortex Cinnamomi; Radix Paeonae Rubra; Pollen Typhae; Faeces Trogopterorum | Promoting blood circulation and removing blood stasis, warming meridian, and pain relief | 83 (3.16%)       | 32 (1.22%)           |
| Liu-Wei-Dihuang-wan   | Radix Rehmanniae Preparata; Corni Fructus.; Dioscoreae Rhizoma; Alismatis Rhizoma; Pollen Typhae; Faeces Trogopterorum | Nourishing the liver and kidney                                                          | 57 (2.17%)       | 21 (0.80%)           |
| 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 | Replenishing qi and blood, tonifying the spleen, and nourishing the heart                 | 49 (1.87%)       | 25 (0.95%)           |
| Si-Wu-Tang            | Angelicae sinensis Radix; Rehmanniae Radix; Paeoniae Radix; Ligustici Rhizoma              | Replenishing blood and regulating menstruation                                            | 46 (1.75%)       | 11 (0.42%)           |

#: number of users divided by the number of successful pregnancy/unsuccessful pregnancy.
the loss of menstrual blood. Some of the ingredients of Si-Wu-Tang include Radix Rehmanniae Preparata, Radix Paeoniae Lactiflorae, and Radix Angelicae sinensis. Radix Rehmanniae, which is an important ingredient of diverse TCM formulas, has anti-inflammation and antioxidation effect to alleviate dermatitis [20], autoimmune disease [5], and allergic diseases [6]. Moreover, this compound has an effect on the activation of the parasympathetic nervous system determined by heart rate variability [19].

The goal of the subgroup analysis is to assess whether there exists consistency of or large differences in the magnitude of treatment effect among different subgroups of

| Fertility drugs              | N   | %   | Unadjusted OR (95% CI) | Adjusted OR (95% CI) |
|------------------------------|-----|-----|------------------------|----------------------|
| TCM prescription             |     |     |                        |                      |
| Jia-Wei-Xiao-Yao-San         | 253 | 4.82| 3.47 (2.58, 4.67)***   | 3.17 (2.35, 4.28)*** |
| Wen-Jing-Tang                | 213 | 4.05| 3.15 (2.30, 4.32)***   | 2.83 (2.06, 3.90)*** |
| Dang-Gui-Sha-Yao-San         | 207 | 3.94| 3.37 (2.43, 4.66)***   | 3.14 (2.26, 4.37)*** |
| Zou-Gui-Wan                  | 152 | 2.89| 2.69 (1.88, 3.85)***   | 2.47 (1.71, 3.56)*** |
| Gui-Zhi-Fu-Ling-Wan          | 127 | 2.42| 3.64 (2.38, 5.55)***   | 3.27 (2.13, 5.02)*** |
| You-Gui-Wan                  | 115 | 2.19| 2.33 (1.56, 3.47)***   | 2.12 (1.41, 3.18)*** |
| Shao-Fu-Zhu-Yu-Tang          | 115 | 2.19| 2.64 (1.75, 3.99)***   | 2.54 (1.67, 3.86)*** |
| Liu-Wei-Dihuang-Wan          | 78  | 1.48| 2.75 (1.66, 4.55)***   | 2.52 (1.51, 4.21)*** |
| Gui-Pi-Tang                  | 74  | 1.41| 1.98 (1.22, 3.21)**    | 1.69 (1.04, 2.77)*   |
| Si-Wu-Tang                   | 57  | 1.08| 4.24 (2.19, 8.20)****  | 4.25 (2.18, 8.30)**  |
| Western medicine             |     |     |                        |                      |
| Clomiphene citrate/tamoxifen | 1299| 24.72| 3.87 (3.37, 4.44)***   | 3.76 (3.26, 4.34)*** |
| GnRH agonist/GnRH antagonist | 2   | 0.04| —                      | —                    |
| Progesterone                 | 290 | 5.52| 3.34 (2.54, 4.39)***   | 3.22 (2.44, 4.26)*** |
| Bromocriptine/cabergoline    | 147 | 2.80| 3.06 (2.10, 4.46)***   | 2.94 (2.00, 4.32)*** |

OR: odd ratio; 95% CI: 95% confidence interval; TCM: traditional Chinese medicine; * p < 0.05; ** p < 0.01; *** p < 0.001. #: number of users divided by the total sample size. Multivariate-adjusted for age at diagnosis, insured amount, urban level, residential area, insured unit, and comorbidities.

Figure 2: The odds ratios of pregnancy stratified by polycystic ovary syndrome, endometriosis, irregular menstrual cycle, uterine fibroids, and dysmenorrhea.
patients. It provides more precise findings when the health professionals applied these results to patients in clinical practice. The results of our subgroup analysis found that the association between TCM use and successful pregnancy is only consistent across categories of regular and irregular menstrual cycles. The association between TCM and successful pregnancy was not significant in women with polycystic ovary syndrome, endometriosis, or dysmenorrhea even though the magnitude of OR was slightly larger than or similar to those in women without these corresponding comorbidities. These results may be due to small sample size for women with polycystic ovary syndrome, endometriosis, or dysmenorrhea. It seems that uterine fibroids exert antagonistic interaction on TCM use and successful pregnancy although this interaction is not significant. To provide this association in infertile women with these comorbidities, a larger scale study is needed. Given the results of the subgroup analysis, our study’s findings may not be generalized into a larger scale study. Given the results of the subgroup analysis, our study’s findings may not be generalized into a larger scale study.

An animal study first demonstrated that Dang-Gui-Sha-Yao-San improved depression-like behavior, such as increased open-field activities, shortened immobility time, and percentage of sugar preference compared with the stress control group by the potential mechanisms of decreasing central arginine vasopressin and the expression of AVP mRNA [21]. In an in vitro study using rat uterine smooth muscle, Dang-Gui-Sha-Yao-San also had its antagonistic effect on contraction caused by KCL depolarization dysmenorrhea by suppressing smooth muscle contractions of uterine [22]. In addition, Dang-Gui-Sha-Yao-San had been shown in vivo that women with luteal insufficiency, which was determined by the daily measurement of basal body temperature and plasma progesterone levels, had improved their insufficiency for luteal phase [23]. In an observational study of 39 consecutive patients with climacteric disorders diagnosed by the Kupperman index, the administration of hormone replacement therapy for infertile women. The results suggested that TCM was used as an adjunctive therapy is common for infertility. The results suggested that TCM was associated with higher likelihood of the successful pregnancy in infertile women, which is worthy of further investigation by randomized control trial. Our study suggests that TCM may be used in clinical management for treating female infertility.

5. Conclusions

We demonstrated TCM as an adjunctive therapy is common for infertility women. The results suggested that TCM was associated with higher likelihood of the successful pregnancy in infertile women, which is worthy of further investigation by randomized control trial. Our study suggests that TCM may be used in clinical management for treating female infertility.

Abbreviations

TCM: Traditional Chinese medicine  
CHP: Chinese herbal product  
NHI: National Health Insurance  
NHIRD: National Health Insurance Research Database  
ICD-9-CM: International Classification of Diseases, Ninth Revision, Clinical Modification  
LHD2000: Longitudinal Health Insurance Database 2000  
GnRH: Gonadotropin-releasing hormone  
ORs: Odds ratios  
CIs: Confidence intervals.
Data Availability
The data used to support the findings of this study are included within the article.

Conflicts of Interest
The authors declare that they have no conflicts of interest.

Authors’ Contributions
Yueh-Hsiang Liao and Tsai-Chung Li contributed equally to this work.

Supplementary Materials
Supplementary Materials. Table S1: infertility women’s medication use based on with or without pregnancy status. Table S2: unadjusted and adjusted odds ratios and 95% confidence intervals of successful pregnancy among infertility women for TCM use by excluding women with Western fertility drugs use (n = 3,731). Table S3: unadjusted and adjusted odds ratios of successful pregnancy for individual commonly used fertility drugs by excluding women with Western fertility drugs use (n = 3,731). (Supplementary Materials)

References
[1] M. N. Mascarinho, S. R. Flaxman, T. Boerma, S. Vanderpoel, and G. A. Stevens, “National, regional, and global trends in infertility prevalence since 1990: a systematic analysis of 277 health surveys,” PLoS Med, vol. 9, no. 12, p. e1001356, 2012.
[2] A. Namdar, M. M. Naghizadeh, M. Zamani, F. Yaghmaei, and M. H. Sameni, “Quality of life and general health of infertile women,” Health Qual Life Outcomes, vol. 15, no. 1, p. 139, 2017.
[3] MOI, “Fertility rates of childbearing age women,” https://www.moi.gov.tw/files/site_stuff/321/2/year/year_en.html.
[4] S. Gurunath, Z. Pandian, R. A. Anderson, and S. Bhattacharya, “Defining infertility--a systematic review of prevalence studies,” Human Reproduction Update, vol. 17, no. 5, pp. 575–588, 2011.
[5] WHO, “Recent advances in medically assisted conception. Report of a WHO Scientific Group,” World Health Organization Technical Report Series, vol. 820, pp. 1–111, 1992.
[6] M. S. Abrao, L. Muzii, and R. Marana, “Anatomical causes of female infertility and their management,” International Journal of Gynaecology and Obstetrics, vol. 123, no. Suppl 2, pp. S18–S24, 2013.
[7] J. B. Stanford, J. C. Martin, M. Gibson, E. Birdsall, and D. I. Brixner, “Use of clomiphene citrate in the university of Utah community clinics,” The Journal of Reproductive Medicine, vol. 58, no. 5-6, pp. 229–233, 2013.
[8] R. V. Weiss and R. Clapauch, “Female infertility of endocrine origin,” Arquivos Brasileiros de Endocrinologia & Metabolologia, vol. 58, no. 2, pp. 144–152, 2014.
[9] C. J. See, M. McCulloch, C. Smikle, and J. Gao, “Chinese herbal medicine and clomiphene citrate for anovulation: a meta-analysis of randomized controlled trials,” Journal of Alternative and Complementary Medicine, vol. 17, no. 5, pp. 397–405, 2011.
[10] L. Tan, Y. Tong, S. C. Sze et al., “Chinese herbal medicine for infertility with anovulation: a systematic review,” Journal of Alternative and Complementary Medicine, vol. 18, no. 12, pp. 1087–1100, 2012.
[11] Y. R. Lin, M. Y. Wu, J. H. Chiang, H. R. Yen, and S. T. Yang, “The utilization of traditional Chinese medicine in patients with dysfunctional uterine bleeding in Taiwan: a nationwide population-based study,” BMC Complementary and Alternative Medicine, vol. 17, no. 1, p. 427, 2017.
[12] F. P. Chen, T. J. Chen, Y. Y. Kung et al., “Use frequency of traditional Chinese medicine in Taiwan,” BMC Health Services Research, vol. 7, p. 26, 2003.
[13] Practice Committee of the American Society for Reproductive Medicine, “Definitions of infertility and recurrent pregnancy loss,” Fertility and Sterility, vol. 90, no. 5 Suppl, p. S60, 2013.
[14] Y. C. Hung, C. W. Kao, C. C. Lin et al., “Chinese herbal products for female infertility in Taiwan: a population-based cohort study,” Medicine (Baltimore), vol. 95, no. 11, p. e3075, 2016.
[15] T. H. Chao, P. K. Fu, C. H. Chang, S. N. Chang, F. Chiahung Mao, and C. H. Lin, “Prescription patterns of Chinese herbal products for post-surgery colon cancer patients in Taiwan,” Journal of Ethnopharmacology, vol. 155, no. 1, pp. 702–708, 2014.
[16] Y. H. Liao, C. C. Lin, H. C. Lai, J. H. Chiang, J. G. Lin, and T. C. Li, “Adjuvantive traditional Chinese medicine therapy improves survival of liver cancer patients,” Liver International, vol. 35, no. 12, pp. 2595–2602, 2015.
[17] B. R. Wang, Y. L. Chang, T. J. Chen et al., “Coprescription of Chinese herbal medicine and Western medication among female patients with breast cancer in Taiwan: analysis of national insurance claims,” Patient Prefer Adherence, vol. 8, pp. 671–682, 2014.
[18] T. Ushiroyama, A. Ikeda, K. Sakuma, and M. Ueki, “Changes in serum tumor necrosis factor (TNF-alpha) with kami-shoyo-san administration in depressed climacteric patients,” American Journal of Chinese Medicine, vol. 32, no. 4, pp. 621–629, 2014.
[19] D. M. Park, S. H. Kim, Y. C. Park, W. C. Kang, S. R. Lee, and I. C. Jung, “The comparative clinical study of efficacy of Gamisoyo-San (jiaweixiaoyaosan) on generalized anxiety disorder according to differently manufactured preparations: multicenter, randomized, double blind, placebo controlled trial,” Journal of Ethnopharmacology, vol. 158, no. Pt A, pp. 11–17, 2014.
[20] N. Weeg, E. Shalom-Paz, and A. Wiser, “Age and infertility: the clinical point of view,” Minerva Ginecologica, vol. 64, no. 6, pp. 477–483, 2012.
[21] F. Xu, D. Peng, C. Tao et al., “Anti-depression effects of Danggui-Shaoyao-San, a fixed combination of Traditional Chinese Medicine, on depression model in mice and rats,” Phytomedicine, vol. 18, no. 13, pp. 1130–1136, 2011.
[22] C. S. Hsu, J. K. Yang, and L. L. Yang, “Effect of “Dang-Qui-Shao-Yao-San” a Chinese medicinal prescription for dysmenorrhea on uterus contractility in vitro,” Phytomedicine, vol. 18, no. 12, pp. 671–682, 2011.
[23] T. Ushiroyama, A. Ikeda, K. Sakuma, and M. Ueki, “Changes in serum tumor necrosis factor (TNF-alpha) with kami-shoyo-san administration in depressed climacteric patients,” American Journal of Chinese Medicine, vol. 32, no. 4, pp. 621–629, 2014.
[24] F. P. Chen, T. J. Chen, Y. Y. Kung et al., “Use frequency of traditional Chinese medicine in Taiwan,” BMC Health Services Research, vol. 7, p. 26, 2003.
[13] Practice Committee of the American Society for Reproductive Medicine, “Definitions of infertility and recurrent pregnancy loss,” Fertility and Sterility, vol. 90, no. 5 Suppl, p. S60, 2013.
[14] Y. C. Hung, C. W. Kao, C. C. Lin et al., “Chinese herbal products for female infertility in Taiwan: a population-based cohort study,” Medicine (Baltimore), vol. 95, no. 11, p. e3075, 2016.
[25] L. Sun, L. Liu, S. Zong et al., “Traditional Chinese medicine Guizhi Fuling capsule used for therapy of dysmenorrhea via attenuating uterus contraction,” *Journal of Ethnopharmacology*, vol. 191, pp. 273–279, 2016.